Tuning Stereoselection in Tethered Biginelli Condensations. Synthesis of *cis*- or *trans*-1-Oxo- and 1-Iminohexahydropyrrolo[1,2-*c*]pyrimidines

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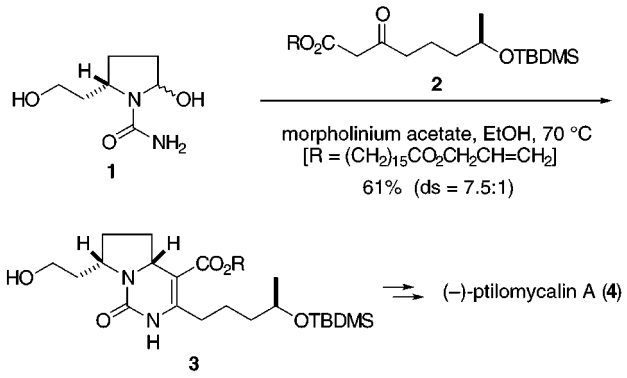
Stereoselection in tethered Biginelli condensations can be tuned to give either the cis or trans stereoisomer of 1-oxohexahydropyrrolo[1,2-*c*]pyrimidine and 1-iminohexahydropyrrolo[1,2-*c*]pyrimidine products (see eq 1). With substrates having urea and *N*-sulfonylguanidine functionality (Schemes 2 and 4), cis stereoselection (4−7:1) is observed when the condensation is accomplished under Knoevenagel conditions, while trans stereoselection (4−20:1) is observed when the condensation is carried out in the presence of polyphosphate ester (PPE). Under both conditions, steroselectivity is highest in the *N*-sulfonylguanidine series. With substrates bearing a basic guanidine unit, the trans product is formed exclusively under Knoevenagel conditions (Scheme 3).

Introduction

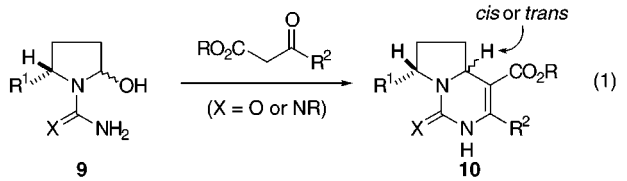
In 1893, Biginelli reported the synthesis of dihydropyrimidines from the condensation of ethyl acetoacetate, aromatic aldehydes, and urea.[1] Since Biginelli's initial disclosure, variations in all three components have led to the synthesis of an array of functionalized dihydropyrimidines and analogues.[2] We reported in 1993 the first intramolecular variant of the Biginelli condensation by connecting the aldehyde and urea functionalities with a tether of three carbons.[3] Under Knoevenagel conditions, tethered Biginelli reactions of this type proceed with moderate to good stereoselectivity to form *cis*-1-oxohexahydropyrrolo[1,2-*c*]pyrimidine products (Scheme 1).[4] These condensations represented the first use of the Biginelli reaction in stereocontrolled organic synthesis. Moreover, the utility of this tethered variant of the Biginelli condensation for natural products total synthesis was verified by use of **3** to achieve the first total synthesis of a crambescidin alkaloid, (−)-ptilomycalin A (**4**).[4]

In addition to ptilomycalin A (**4**), numerous other marine alkaloids having a hydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate part structure have been isolated (Figure 1). Representative are (a) crambescidin alkaloids[5] such as crambescidin 816 (**5**) and isocrambescidin 800 (**6**) for which a variety of pharmacological activities have been described, including in vitro anticancer activity,[5ac] inhibition of calcium channels,[5d] and inhibition of Na^+, K^+- and Ca^{2+}-ATPases,[6] and (b) batzelladine alkaloids, exemplified by batzelladines B (**7**) and D (**8**),[7] which are reported to modulate protein−protein interactions that are important for immunological responses.[7ab]

Scheme 1



Apparent in the alkaloids depicted in Figure 1 is the occurrence of the hydropyrrolo[1,2-*c*]pyrimidine unit with either the syn or anti relationship of the hydrogens flanking the pyrrolidine nitrogen. We therefore became interested in the possibility of modifying the stereoselectivity of tethered Biginelli condensations to also gain access to hexahydropyrrolopyrimidines **10** having the trans stereochemistry (eq 1). In addition, we sought to



(1)

(1) Biginelli, P. (*Gazz. Chem. Ital.* **1893**, *23*, 360.
(2) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
(3) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235.
(4) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657.
(5) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (c) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472. (d) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. (e) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007. (f) Tavares, R.; Daloze, D.; Braekman, J. C.; Hajdu, E.; Muricy, G.; Van Soest, R. W. M. *Biochem. Syst. Ecol.* **1994**, *22*, 645. (g) Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carre, J. B.; Debitus, C.; Lucarain, L.; Provost, J. *Tetrahedron* **1995**, *51*, 3675.
(6) Ohizumi, Y.; Sasaki, S.; Kusumi, T.; Ohtani, I. I. *Eur. J. Pharmacol.* **1996**, *310*, 95.
(7) (a) Patil, A. D.; Kumar, N. V; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Derosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182. (b) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814. (c) Patil, A. D.; Freyer, A. J.; Offen, P.; Bean, M. F.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 704.

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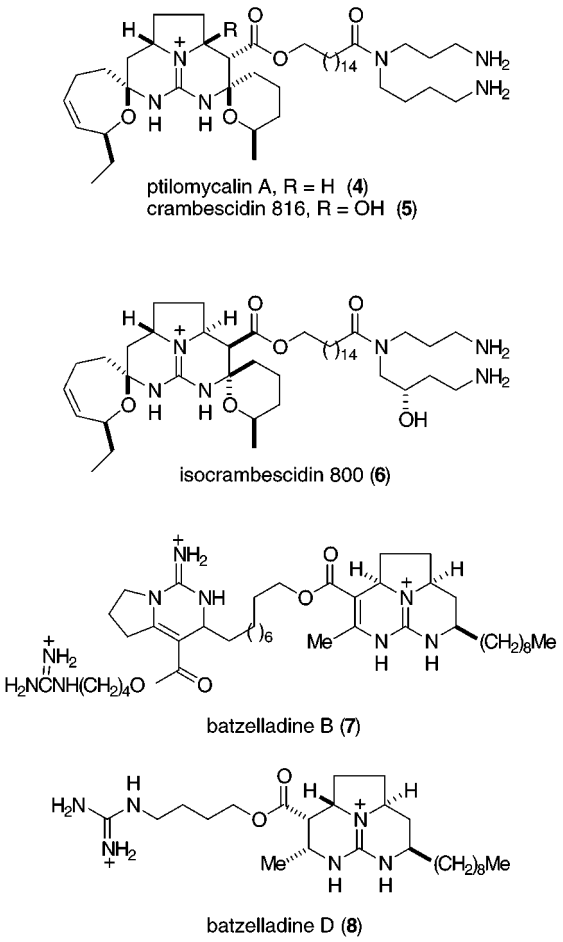


Figure 1. Representative crambescidin and batzelladine alkaloids.

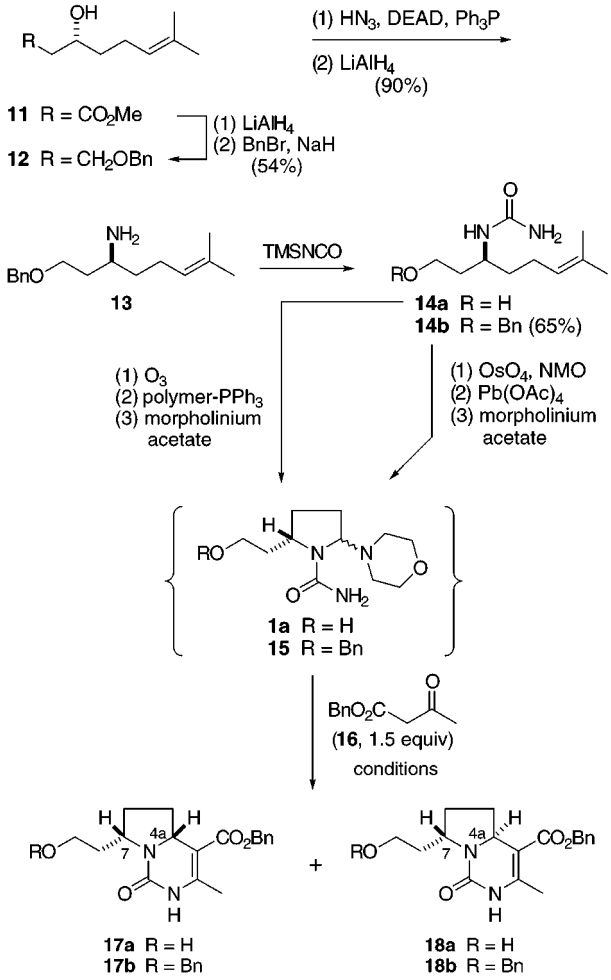
develop methods for directly preparing hexahydropyrrolopyrimidines **10** containing guanidine functionality (X = NR), since properly functionalized intermediates of this sort might efficiently meld into the more elaborate guanidine ring systems of the crambescidin and batzelladine alkaloids.

Results and Discussion

Biginelli Condensations of Tethered Ureido Aldehydes. To pursue whether the free hydroxyl group in **1** might be influencing stereoselection, Biginelli condensations of this intermediate and benzyl ether derivative **15** were examined (Scheme 2). Like **1**,[3] the benzyl ether congener was accessed from (*R*)-methyl-3-hydroxy-7-methyl-6-octenoate (**11**).[8] Reduction of **11** with $LiAlH_4$ and selective monobenzylation of the resulting diol by reaction with excess NaH and benzyl bromide in DMF at −40 to −10 °C furnished **12**. Mitsunobu inversion of alcohol **12** with HN_3,[9] followed by reduction of the resulting azide and reaction of the resulting primary amine with trimethylsilyl isocyanate, provided urea **14b** in 32% overall yield from **11**.

In our earlier studies, the double bond of **14a** had been cleaved with ozone, using a dimethyl sulfide workup, to generate **1**.[3,4] In the current investigation, we found that

Scheme 2



substrate	reaction conditions	**17**:**18** (yield)[a]
1a	morpholinium acetate (1.5 eq), CF_3CH_2OH, 60 °C, 48 h	4:1 (80%)
15		4:1 (81%)
15	PPE, CH_2Cl_2, 23 °C, 48 h	1:4 (60%)

[a] Combined overall yield of **17** and **18** from **14**.

this procedure was not reliable and in various runs generated intermediates that condensed with benzyl acetoacetate (**16**) in widely variable yields. Mass spectral data for **1** generated in this way indicated the presence of many higher molecular weight oligomers. A more reproducible procedure was to add 1.5 equiv of morpholinium acetate to the crude reaction mixture after reductive workup of the ozonide, but prior to concentration. Replacing dimethyl sulfide with polymer-bound triphenylphosphine eliminated contamination with DMSO. Mass spectral data of the product **1a** generated in this fashion indicated incorporation of morpholine (with loss of H_2O) and showed the virtual absence of higher molecular weight oligomers. Alternatively, **15** was generated by dihydroxylation of the corresponding alkene precursor, followed by cleavage of the derived 1,2-diol with $Pb(OAc)_4$.[10] Aminals **1a** and **15** were never subjected to an aqueous workup or purification, but rather were used directly following removal of either the phosphine polymer or lead salts by filtration and concentration of the filtrate after adding morpholinium acetate. These intermediates are not simply a mixture of stereoisomers, but at least three components as judged by ^1H and ^{13}C NMR

(8) Kitamuram, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.
(9) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.

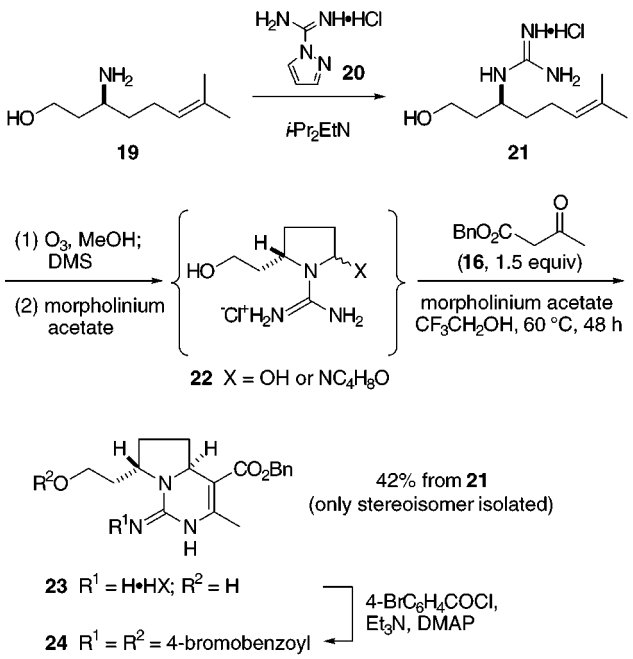
data; multiple signals are observed for many carbon atoms in the ^{13}C NMR spectra, while broad peaks are seen in the ^{1}H NMR spectra and no aldehyde signal is apparent.

Biginelli condensations of crude **15** or **1a** (generated from 1 equiv of **14a** or **14b**) were carried out under identical conditions by reaction with 1.5 equiv of β-ketoester **16** and 1.5 equiv of morpholinium acetate at 60 °C in 2,2,2-trifluoroethanol. These conditions provided the *cis*- and *trans*-1-oxohexahydropyrrolo[1,2-*c*]pyrimidines **17a** and **18a** in a 4:1 ratio (80% yield) and the corresponding benzyl ether analogues **17b** and **18b** in an identical 4:1 ratio (81% yield). The β-oxygen substituent of the side chain clearly plays no significant role. Trifluoroethanol was employed as the reaction solvent since earlier studies with related intermediates had shown that cis stereoselection under Knoevenagel conditions was optimal in this highly polar solvent. For example, stereoselection in the condensation of **1** and **16** was 2:1 when ethanol was employed. Products **17a** and **18a** did not interconvert upon resubmission to reaction conditions. Stereochemical assignments for the hexahydropyrrolo-[1,2-*c*]pyrimidine products followed from diagnostic ^{1}H NMR signals of the angular methine hydrogens H4a and H7: **17a** (4.25 and 4.11 ppm) and **17b** (4.29 and 4.00 ppm).[3]

In a recent investigation, Kappe reported[11] that the mild dehydrating agent polyphosphate ester (PPE)[12] was an excellent promoter of the classical three-component Biginelli condensation. Condensation of **15** with β-ketoester **16** at room temperature in a 1:1 mixture of PPE and CH_2Cl_2 provided Biginelli products **17b** and **18b** in 60% yield, with the trans isomer **18b** now predominating to the extent of 4:1. Identical to what was observed under Knoevenagel conditions, **17b** and **18b** were recovered unchanged when resubmitted to the PPE reaction conditions for 48h.

Biginelli Condensations of Tethered Guanyl Aldehydes. Although three-component condensations of guanidines, aldehydes, and β-ketoesters are known, this modification of the Biginelli condensation has not been widely explored.[2] To examine the tethered variant, unsaturated guanidinium alcohol **21** was prepared from (*S*)-amino alcohol **19**[4] by condensation with 1*H*-pyrazole-1-carboxamidine hydrochloride (**20**) (Scheme 3).[13] Ozonolysis of **21** followed by workup with dimethyl sulfide and concentration provided **22**, which like its urea counterpart was a mixture of several components. When **22** was concentrated with 1.5 equiv of morpholinium acetate, FAB mass spectral data indicated incorporation of morpholine with loss of H_2O; higher molecular weight oligomers were not observed for either **22** (X = OH) or its morpholine adduct. Both intermediates performed identically in Biginelli condensations. Without purification, **22** was condensed with β-keto ester **16**, using Knoevenagel conditions identical to those employed in the urea series, to afford a single Biginelli adduct **23** in 42% overall yield from **19**. To our delight, this product

Scheme 3



had the trans stereochemistry as rigorously established by single-crystal X-ray analysis of dibenzoyl derivative **24**.[14]

To pursue the origin of the stereochemical reversal in the urea and guanidine series, we next investigated Biginelli condensations of tethered *N*-sulfonylguanidine aldehydes **26** (Scheme 4). Since the pK_a of *N*-sulfonylguanidinium salts is typically ~1, the sulfonylguanidine substituent electronically resembles more closely a urea than a guanidine.[15,16] Treatment of amino alcohol **19**, or the corresponding amino ether **13**, with *S*,*S*,-dimethyl *N*-(4-methoxy-2,3,6-trimethylbenzenesulfonyl)-carbonimidodithioate, followed by aminolysis with NH_3 and $AgNO_3$, afforded the Mtr-protected guanidines **25** in good yield.[17] Dihydroxylation of these intermediates, followed by diol cleavage, provided **26a** and **26b**. These intermediates were again not simple mixtures of stereoisomers; multiple signals were observed for many carbon atoms in the ^{13}C spectra, while the ^{1}H spectra exhibited broad peaks and showed no apparent aldehyde signal.

Biginelli condensation of crude **26b** with β-keto ester **16** under Knoevenagel conditions identical to those employed with the other substrates proceeded in 84% yield to give the *cis*- and *trans*-1-iminohexahydropyrrolopyrimidines **27b** and **28b** in a 7:1 ratio. Nearly identical stereoselectivity was realized in the hydroxyethyl series. In dramatic contrast, when the condensation of **26b** and **16** was carried out with PPE, the *trans*-1-iminohexahy-

(10) Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032.

(11) (a) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201. (b) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.

(12) Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665.

(13) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.

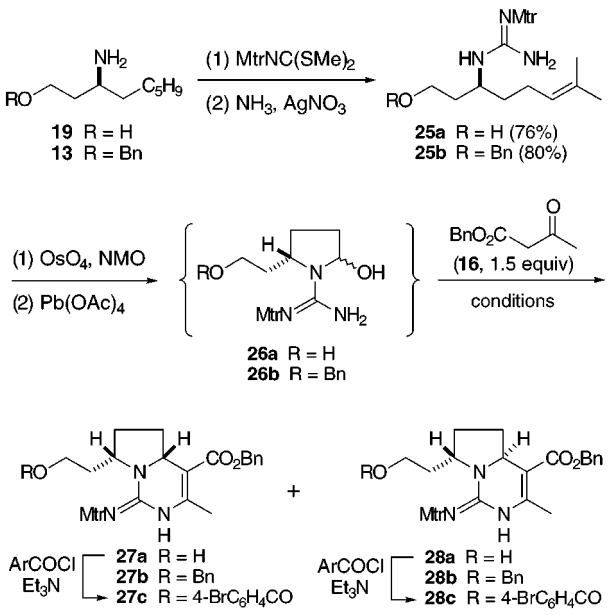
(14) The authors have deposited coordinates for compound **24** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(15) The statistically corrected pK_a of a monosubstituted guanidinium salt bearing an SO_2NH_2 substituent has been determined to be 1.83 in water.[16a] Using the linear free energy correlation developed in this paper,[16a] the value for the corresponding SO_2Me-substituted guanidinium salt would be 0.2.

(16) (a) Tatlor, P. J.; Wait, A. R. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1765. (b) For a brief discussion of guanidine basicity, see: Yamamoto, Y.; Kojima, S. *Synthesis and Chemistry of Guanidine Derivatives*; Yamamoto, Y., Kojima, S., Ed., Wiley: New York, 1991; Vol. 2, pp 485−526.

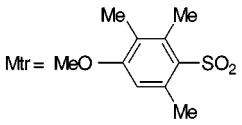
(17) Burgess, K.; Lim, D.; Ho, K.; Ke, C. J. *J. Org. Chem.* **1994**, *59*, 2179.

Scheme 4



substrate	reaction conditions	**27**:**28** (yield)[a]
26a	morpholinium acetate (1.5 eq),	6:1 (61%)
26b	CF_3CH_2OH, 60 °C, 48 h	7:1 (84%)
26b	PPE, CH_2Cl_2, 23 °C, 48 h	1:20 (61%)

[a] Combined overall yield of **27** and **28** from **25**.



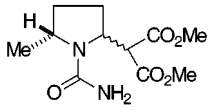
dropyrrolopyrimidine **27b** predominated to the extent of 20:1. Sulfonylguanidine products **27b** and **28b** were recovered unchanged when resubmitted for 48 h to either the Knoevenagel or PPE reaction conditions.

Stereochemical assignments were made by chemical correlation of **28a** with **24**. Acylation of the crude product mixture produced from Biginelli condensation of **26a** and **16** under Knoevenagel conditions with 4-bromobenzoyl chloride followed by separating the isomers by HPLC provided pure samples of **27c** and **28c**. Exposure of the minor product **28c** to TFA at room temperature removed the Mtr group, and acylation of the resulting free guanidine with 4-bromobenzoyl chloride provided **24**.

Discussion

This study demonstrates that stereoselection in tethered Biginelli condensations to form 1-oxo- and 1-iminohexahydropyrrolo[1,2-*c*]pyrimidines varies substantially depending on reaction conditions and the nature of the group X (eq 1). With substrates having urea and *N*-sulfonylguanidine functionality, cis stereoselection (4−7:1) is observed when the condensation is accomplished under Knoevenagel conditions, while trans stereoselection (4−20:1) is observed when the condensation is carried out in the presence of polyphosphate ester (PPE). Under both conditions, steroselectivity was highest in the *N*-sulfonylguanidine series. With a substrate having a basic guanidine unit, the trans product is formed exclusively under Knoevenagel conditions. Since the Knoevenagel conditions are notably mild (morpholinium acetate in CF_3CH_2OH at 60 °C), this latter guanyl aldehyde route to *trans*-1-iminohexahydropyrrolo[1,2-*c*]pyrimidines will likely be particularly useful for the synthesis of crambescidin and batzelladine alkaloids having the anti relationship of the hydrogens flanking the pyrrolidine nitrogen.[18]

Since the various steps in the tethered Biginelli condensations reported here and earlier[3,4] have yet to be studied individually, we can only speculate at this time about the origin of stereoselectivity. As a framework for future mechanistic studies, we proffer the following working hypothesis (Figure 2). Under Knoevenagel conditions, the stereochemistry-determining step in condensations of ureido or *N*-sulfonylimino aldehyde intermediates **29** could be cyclization of Knoevenagel adduct **31** to give **33**. If this reaction has a late transition state, the



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cis-2,5-disubstituted pyrrolidine should be formed preferentially.[19,20] In contrast, in the guanyl aldehyde series, loss of HY from **29** to form the corresponding iminium ion **30** should be particularly favorable, since the nitrogen substituent in **30** is a weakly electron-withdrawing amidine group. If addition of the enol (or enamine) derivative of **16** is controlled primarily by destabilizing interactions with the side chain,[21] trans adduct **32** should be produced preferentially in what could be the stereochemistry-determining step. Alternatively, the stereochemistry-determining step could be [4 + 2]-cycloaddition of the enol (or enamine) or **30** from the face opposite the side chain, followed by loss of water (or morpholine). In accord with Kappe's recent investigations of the mechanism of the three component Biginelli reaction under classical acidic conditions,[11] we suggest that condensations of the ureido or *N*-sulfonylimino aldehyde intermediates **29** in the presence of polyphosphate ester (PPE) could also proceed by the iminium ion pathway to provide largely *trans*-1-oxo- and 1-iminohexahydropyrrolo[1,2-*c*]-pyrimidines.

Conclusion

As we had hoped at the outset of this investigation, stereoselection in the tethered Biginelli condensations

(18) The first total synthesis of isorambescidin 800 (**6**) has recently been accomplished using this approach: Coffey, D. S.; McDonald, A. I.; Overman, L. E., Stappenbeck, F. Submitted for publication.

(19) Molecular mechanics calculations on the model *N*-acylamino-2,5-disubstituted pyrrolidines **36** show that the cis isomer is 1.9 kcal/mol more stable than the trans isomer.[20]

(20) Calculations were done using the MM2* force field and the Monte Carlo search routine of MacroModel V3.5X.

(21) In an elegant study, Seebach and co-workers have shown that face selection in the reaction of *N*-acyliminium ions related to **30** with small nucleophiles is controlled by pyramidalization of the acyl group and provides largely the cis-2,5-product.[22] However, there is at least one report that when the nucleophile is large, the trans product dominates.[23]

(22) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913 and references cited therin.

(23) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011.

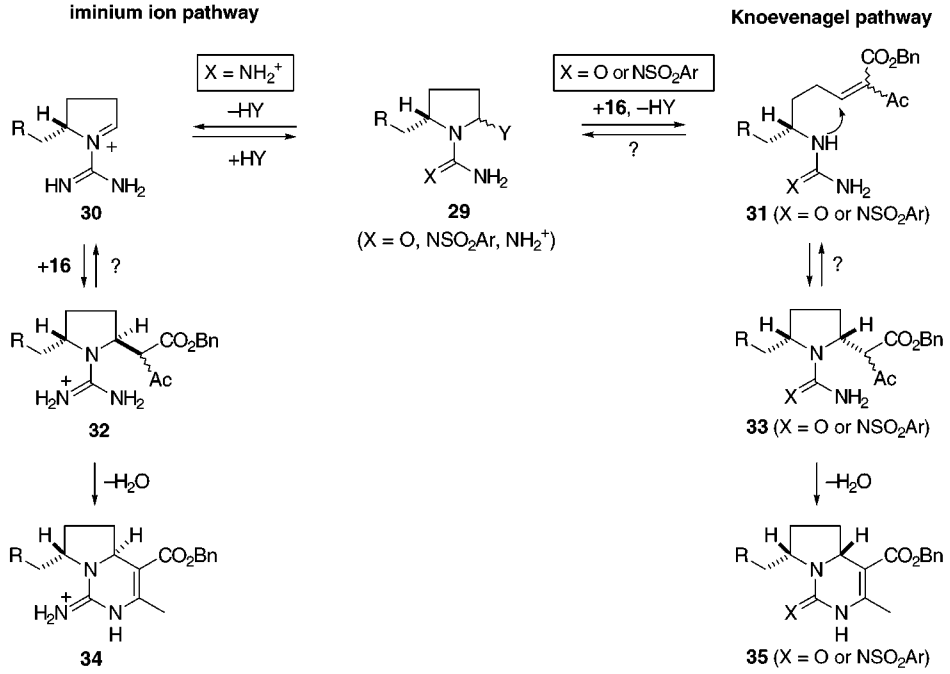

Figure 2. Two mechanistic possibilities for tethered Biginelli condensations under Knoevenagel conditions (Y = OH or NR_2).

depicted in eq 1 can be tuned to give either the cis or trans product. Under optimum conditions, the trans isomer can be obtained in high stereoselectivity (>20:1) and the cis isomer in moderate selectivity (4−7:1).[4] We have also extended tethered Biginelli condensations to include guanyl aldehyde substrates that produce Biginelli products, which should prove particularly useful for preparing complex guanidines. Detailed mechanistic studies will be required to clarify stereochemical control elements in tethered Biginelli condensations.

Tethered Biginelli condensations have already proved to be powerful reactions for the construction of crambescidin[4,18] and batzelladine alkaloids.[24] Additional applications of the utility of this strategy level reaction for the synthesis of complex guanidines will be reported shortly.

Experimental Section[25]

(*R*)-Benzyloxy-7-methyloct-6-en-3-ol (12). A solution of (*R*)-methyl-3-hydroxy-7-methyl-6-octenoate[8] (21.5 g, 0.115 mol) and Et_2O (100 mL) was added dropwise to a 0 °C suspension of $LiAlH_4$ (6.8 g, 0.18 mol) and Et_2O (0.5 L). After 1 h, H_2O (6.8 mL), 3 M NaOH (6.8 mL), and H_2O (20.4 mL) were added sequentially. The resulting mixture was filtered through a pad of Celite, the filtrate was concentrated, and the resulting oil was purified on silica gel (1:1 hexanes−EtOAc) to provide 13.8 g (76%) of (*R*)-7-methyloct-6-ene-1,3-diol as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04−5.08 (m, 1H) 3.82 (s, 2H) 3.68−3.79 (m, 3H) 1.97−2.05 (m, 2H) 1.59−1.67 (m, 4H) 1.54−1.60 (m, 4H) 1.40−1.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 131.8, 123.8, 70.8, 60.7, 38.3, 37.5, 25.5, 24.1, 17.5 ppm; IR (film) 3356 cm^{-1}; $[\alpha]^{23}_D$ +3.5, $[\alpha]^{23}_{577}$ +4.5, $[\alpha]^{23}_{546}$ +4.7, $[\alpha]^{23}_{425}$ +7.3, $[\alpha]^{23}_{405}$ +8.1, (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.09; H, 11.54.

A solution of (*R*)-7-methyloct-6-ene-1,3-diol (7.00 g, 44.3 mmol) and DMF (80 mL) was added dropwise to a −40 °C suspension of NaH (3.20 g, 133 mmol, prewashed with hexanes 3 × 50 mL) and DMF (130 mL). After 15 min, benzyl bromide (5.30 mL, 44.3 mmol) was added, and the reaction was warmed to −10 °C over 1 h. The reaction was quenched by pouring into saturated aqueous NH_4Cl (300 mL), and the resulting mixture was extracted with Et_2O (4 × 150 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. The crude oil was purified on silica gel (9:1 hexanes−EtOAc to 4:1 hexanes−EtOAc) to provide 7.74 g (71%) of **12** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.36 (m, 4H) 7.26−7.31 (m, 1H) 5.14−5.17 (m, 1H) 4.51 (s, 2H) 3.78−3.83 (m, 1H) 3.66−3.73 (m, 1H) 3.62−3.65 (m, 1H) 3.04 (s, 1H) 2.05−2.16 (m, 2H) 1.73−1.77 (m, 2H) 1.71 (s, 3H) 1.63 (s, 3H) 1.44−1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.8, 131.5, 128.2, 127.5, 127.4, 124.0, 73.0, 70.4, 68.8, 37.3, 36.3, 25.5, 24.0, 17.5 ppm; IR (film) 3443 cm^{-1}; $[\alpha]^{23}_D$ +13.0, $[\alpha]^{23}_{577}$ +13.9, $[\alpha]^{23}_{546}$ +15.6, $[\alpha]^{23}_{435}$ +26.5, $[\alpha]^{23}_{405}$ +31.3 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.25; H, 9.74.

(*S*)-3-Amino-1-benzyloxy-7-methyl-6-octene (13). Diethyl azodicarboxylate (4.12 g, 23.7 mmol) was added dropwise to a solution of **13** (5.05 g, 20.3 mmol), Ph_3P (6.22 g, 23.7 mmol), HN_3 (12 mL, 2.0 M in toluene), and toluene (75 mL) at 0 °C. After 15 min, hexanes (0.2 L) was added, the resulting mixture was filtered through a plug of silica gel (the plug was washed with 30 mL of hexanes), and the eluent was concentrated to yield the crude azide as a slightly yellow oil that was used without further purification.

A solution of this crude azide and Et_2O (20 mL) was added dropwise to a stirred 0 °C suspension of $LiAlH_4$ (0.91 g, 24.0 mmol) and Et_2O (100 mL), and after 15 min the reaction was warmed to room temperature. After 1 h, the reaction was cooled to 0 °C, and H_2O (1 mL), 3 M NaOH (1 mL), and H_2O (3 mL) were added sequentially. The resulting mixture was filtered through a pad of

(24) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512.

(25) General experimental details have been described: Minor, K. P.; Overman, E. *J. Org. Chem.* **1997**, *62*, 6379.

Celite, and the filtrate was concentrated to provide 4.53 g (90%) of amine **13** as a colorless oil that was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.38 (m, 4H) 7.27−7.32 (m, 1H) 5.11−5.14 (m, 1H) 4.52 (s, 2H) 3.56−3.65 (m, 2H) 2.88−2.95 (m, 1H) 2.00−2.12 (m, 2H) 1.74−1.82 (m, 1H) 1.70 (s, 3H) 1.62 (s, 3H) 1.42−1.60 (m, 2H) 1.21−1.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.4, 131.5, 128.3, 127.5, 127.4, 124.1, 72.9, 68.1, 48.8, 38.4, 37.6, 25.6, 24.6, 17.6 ppm; IR (film) 3366 cm^{-1}; $[\alpha]^{23}_D$ -3.3, $[\alpha]^{23}_{577}$ −2.7, $[\alpha]^{23}_{546}$ −3.2, $[\alpha]^{23}_{435}$ −4.9, $[\alpha]^{23}_{405}$ −6.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{25}NO\cdot HCl$: C, 67.71; H, 9.23; N, 4.93. Found: C, 67.68; H, 9.27; N, 5.00.

(*S*)-1-Benzyloxy-7-methyl-3-ureido-6-octene (14b). Trimethylsilyl isocyanate (0.90 mL, 6.7 mmol) was added to a solution of crude **13** (1.15 g, 4.65 mmol) and *i*-PrOH (7 mL) at room temperature. After 4 h, the reaction was concentrated, and the resulting oil was purified on silica gel (3:1 hexanes−EtOAc to EtOAc) to provide 873 mg (65%) of **14b** as a colorless solid: mp 79−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.36 (m, 5H) 5.45 (s, 1H) 5.08−5.11 (m, 1H) 5.93 (s, 2H) 4.94 (s, 2H) 3.53−3.63 (m, 3H) 2.05 (m, 2H) 1.83−1.90 (m, 1H) 1.69 (s, 3H) 1.60 (m, 4H) 1.42−1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.4, 138.0, 131.8, 128.3, 127.6, 127.5, 123.6, 72.9, 67.3, 47.9, 35.7, 35.3, 25.6, 24.4, 17.6 ppm; IR (film) 3340, 1653, 1602 cm^{-1}; $[\alpha]^{23}_D$ +16.0, $[\alpha]^{23}_{577}$ +17.3, $[\alpha]^{23}_{546}$ +19.6, $[\alpha]^{23}_{435}$ +34.5, $[\alpha]^{23}_{405}$ +42.6 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.39; H, 9.09; N, 9.55.

Conversion of 14a to Intermediate 1a with Ozone. Ozone was bubbled through a solution of urea **14a** (120 mg, 0.60 mmol), CH_2Cl_2 (5 mL), and MeOH (1 mL) at −78 °C until the solution was saturated (blue color appeared and persisted for 10 min). Nitrogen was then bubbled through the solution to remove excess ozone, Ph_3P−polystyrene (550 mg, 3 mmol P/g resin) was added, and the reaction was allowed to warm to room temperature. After 2 h, the reaction mixture was filtered, morpholinium acetate (140 mg, 0.90 mmol) was added to the filtrate, and the resulting solution was concentrated to give a colorless oil that was used without further purification.[26]

Representative Procedure for Biginelli Condensation under Knoevenagel Conditions. Conversion of 1a to 17 and 18a. A solution of crude aminal **1a** (0.60 mmol), benzyl acetoacetate (0.16 mL, 0.90 mmol), morpholinium acetate (140 mg, 0.90 mmol), and 2,2,2-trifluoroethanol (0.6 mL) was maintained at 60 °C for 2 d. After being cooled to room temperature, the reaction was partitioned between Et_2O (20 mL) and 50% aqueous NH_4Cl (5 mL). The layers were separated, the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The resulting oil was purified on silica gel (2:1 hexanes−EtOAc to 1:1 hexanes−EtOAc) to give 126 mg (64%) of **17a** and 32 mg (16%) of **18a**.

(4a*R*,7*S*)-7-(2-Hydroxyethyl)-3-methyl-1-oxo-1,2,-4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (17a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H) 7.29−7.35 (m, 5H) 5.10−5.20 (m, 2H) 4.25 (dd, J = 11.3, 4.7 Hz, 1H) 4.11 (dd, J = 13.8, 8.2 Hz, 1H) 3.84 (s, 1H) 3.56 (m, 2H) 2.43−2.48 (m, 1H) 2.22 (s, 3H) 2.02−2.08 (m, 1H) 1.81−1.87 (m, 1H) 1.65−1.74 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.6, 154.9, 149.3, 135.9, 128.5, 128.3, 128.1, 102.2, 65.9, 59.0, 58.4, 52.2, 39.3, 30.6, 29.8, 18.0 ppm; IR (film) 3356, 1707, 1673, 1627 cm^{-1}; $[\alpha]^{23}_D$ −26.5, $[\alpha]^{23}_{577}$ −26.8, $[\alpha]^{23}_{546}$ −37.1, $[\alpha]^{23}_{435}$ −119, $[\alpha]^{23}_{405}$ −184 (*c* 1.00, $CHCl_3$); HRMS (CI) *m*/*z* 331.1657 (MH, 331.1658 calcd for $C_{18}H_{23}N_2O_4$).

(4a*S*,7*S*)-7-(2-Hydroxyethyl)-3-methyl-1-oxo-1,2,-4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (18a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H) 7.30−7.38 (m, 5H) 5.12−5.22 (m, 2H) 4.42 (m, 1H) 4.35 (dd, J = 10.2, 4.5 Hz, 1H) 4.33−4.44 (br s, 1H) 3.60 (m, 2H) 2.40−2.45 (m, 1H) 2.45 (s, 3H) 2.06−2.10 (m, 1H) 1.76−1.84 (m, 1H) 1.39−1.55 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.8, 153.0, 146.0, 136.1, 128.6, 128.6, 128.1, 99.1, 65.9, 58.9, 57.3, 53.6, 38.3, 34.9, 28.2, 18.3 ppm; IR (film) 3377, 3232, 1713, 1682, 1633 cm^{-1}; $[\alpha]^{23}_D$ −29.2, $[\alpha]^{23}_{577}$ −29.0, $[\alpha]^{23}_{546}$ −31.0, $[\alpha]^{23}_{435}$ −30.2 (*c* 1.05, $CHCl_3$); HRMS (CI) *m*/*z* 331.1629 (MH, 331.1658 calcd for for $C_{18}H_{23}N_2O_4$). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48.

Represenative Procedure for Generating Tethered Biginelli Precursors by Dihydroxylation and 1,2-Diol Cleavage. Conversion of 14b to 15. Osmium tetroxide (0.4 mL, 0.1 M in *t*-BuOH) was added to a solution of **14b** (120 mg, 0.41 mmol), *N*-methylmorpholine *N*-oxide (230 mg, 1.96 mmol), pyridine (30 mL, 0.4 mmol), and 10:1 THF−H_2O (8 mL). After 30 min, Florisil (1 g), $NaHSO_3$ (1 g), and EtOAc (20 mL) were added, and the resulting mixture was stirred. After 30 min, the reaction mixture was filtered, and the filtrate was concentrated to provide the corresponding 1,2-diol as a colorless oil that was used without further purification.

A solution of this crude diol, $Pb(OAc)_4$ (0.21 g, 0.48 mmol), and CH_2Cl_2 (8 mL) was maintained for 30 min at room temperature. The reaction mixture was then filtered through a plug of Celite, morpholinium acetate (92 mg, 0.62 mmol) was added to the filtrate, and this solution was concentrated to provide crude aminal **15** as a slightly yellow oil.[26]

Conversion of 15 to 17b and 18b under Knoevenagel Biginelli Conditions. Following the representative procedure for Biginelli condensation under Knoevenagel conditions, crude aminal **15** (0.41 mmol) was condensed with **16**, and the crude product was purified on silica gel (2:1 hexanes−EtOAc to 1:1 hexanes−EtOAc) to provide 140 mg (81%) of a 4:1 mixture of **17b** and **18b**. The isomers were separated by medium-pressure liquid chromatography (MPLC) on silica gel (2:1 hexanes−EtOAc to 1:1 hexanes−EtOAc).

(4a*R*,7*S*)-7-(2-Benzyloxyethyl)-3-methyl-1-oxo-1,2,-4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (17b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H) 7.25−7.38 (m, 10H) 5.11−5.21 (m, 2H) 4.43−4.53 (m, 2H) 4.28−4.31 (m, 1H) 3.98−4.02 (m, 1H) 3.51−3.55 (m, 2H) 2.43−2.48 (m, 1H) 2.22−2.28 (m, 1H) 2.20 (s, 3H) 1.86−1.95 (m, 2H) 1.74−1.78 (m, 1H) 1.61−1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.9, 152.7, 148.9, 138.4, 136.1, 128.5, 128.3, 128.3, 128.1, 127.5, 127.4, 101.4, 72.6, 67.8, 65.8, 58.0, 54.4, 33.4, 30.6, 28.9, 18.2 ppm; IR (film) 1682, 1633 cm^{-1}; $[\alpha]^{23}_D$ −18.7, $[\alpha]^{23}_{577}$ −20.3, $[\alpha]^{23}_{546}$ −25.0, $[\alpha]^{23}_{435}$ −71.7, $[\alpha]^{23}_{405}$ −108 (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.31; H, 6.80; N, 6.69.

(4a*S*,7*S*)-7-(2-Benzyloxyethyl)-3-methyl-1-oxo-1,2,-4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (18b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H) 7.33−7.40 (m, 9H) 7.26−7.32 (m,

(26) A copy of the ^{13}C NMR spectrum for this intermediate can be found in the Supporting Information.

1H) 5.14−5.24 (m, 2H) 4.47−4.56 (m, 2H) 4.33−4.41 (m, 2H) 3.60−3.62 (m, 2H) 2.42−2.47 (m, 1H) 2.26 (s, 3H) 2.00−2.12 (m, 2H) 1.73−1.79 (m, 1H) 1.44−1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.0, 151.8, 147.1, 138.4, 136.3, 128.4, 128.2, 128.0, 127.9, 127.5, 127.4, 98.2, 72.8, 67.7, 65.5, 57.2, 54.6, 35.2, 34.8, 28.1, 18.2 ppm; IR (film) 1681, 1640 cm^{-1}; $[\alpha]^{23}_{D}$ −37.5, $[\alpha]^{23}_{577}$ −37.0, $[\alpha]^{23}_{546}$ −39.7, $[\alpha]^{23}_{435}$ −34.5, $[\alpha]^{23}_{405}$ −14.1 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.30; H, 6.73; N, 6.59.

Representative Procedure for Biginelli Condensation in the Presence of PPE. Conversion of 14b to 17b and 18b. Urea **14b** (115 mg, 0.400 mmol) was converted to **15** following the general olefin dihydroxylation and 1,2-diol cleavage procedure. A solution of the resulting crude aminal **15**, benzyl acetoacetate (110 mg, 0.59 mmol), polyphosphate ester (0.2 mL), and CH_2Cl_2 (0.2 mL) was maintained at room temperature for 2 d. The reaction was then quenched by adding Et_2O (20 mL) and 50% aqueous $NaHCO_3$ (5 mL). The layers were separated, the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The resulting oil was purified on silica gel (2:1 hexanes−EtOAc to 1:1 hexanes−EtOAc) to provide a 101 mg (60%) of a 4:1 mixture of **18b** and **17b.**

(4a*S*,7*S*)-7-(2-Hydroxyethyl)-1-imino-3-methyl-1,2,-4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester hydroformate. (23) Following the general procedure of Bernatowicz,[13] a solution of (*S*)-3-amino-7-methyl-6-octenol[4] (0.95 g, 6.0 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (0.95 g, 6.1 mmol), *i*-Pr_2EtN (1.1 mL, 6.3 mmol), and DMF (2.7 mL) was heated at 60 °C. After 4 h, the reaction mixture was concentrated, and the resulting crude **21**, a colorless oil, was used without further purification.

Ozone was bubbled through a solution of this sample of crude **21** and MeOH (25 mL) at −78 °C until the solution was saturated. Nitrogen was then bubbled through the solution to remove excess ozone, Me_2S (1 mL) was added, and the reaction was allowed to warm to room temperature. After 1 h, the reaction mixture was dried ($MgSO_4$) amd filtered, and the filtrate was concentrated to give **22** as a yellow oil that was used without further purification.[26]

Following the representative procedure for Biginelli condensation under Knoevenagel conditions, aminal **22** was condensed with **16** and the crude product was purified on silica gel (100% $CHCl_3$ to 10:1 $CHCl_3$−*i*-PrOH to 10:1:0.1 $CHCl_3$−*i*-PrOH−HCO_2H) to yield 0.95 g (42%) of *trans*-Biginelli product **23** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (br s, 2H) 8.29 (s, 2H) 7.27−7.35 (m, 5H) 5.19 (d, J = 12.3 Hz, 1H) 5.12 (d, J = 12.3 Hz, 1H) 4.28−4.38 (m, 2H) 3.76−3.78 (m, 1H) 3.49−3.53 (m, 1H) 2.45−2.50 (m, 1H) 2.28 (s, 3H) 2.11−2.17 (m, 1H) 1.81−1.87 (m, 1H) 1.58−1.67 (m, 2H) 1.47−1.54 (m, 1H), the OH signal was too broad to observe; ^{13}C NMR (125 MHz, $CDCl_3$) 166.6, 164.9, 150.7, 143.8, 135.5, 128.5, 128.2, 128.1, 101.1, 66.2, 57.1, 56.1, 56.0, 36.0, 34.1, 28.0, 17.2 ppm; IR (film) 3180, 1684, 1572 cm^{-1}; $[\alpha]^{23}_{D}$ −30.7, $[\alpha]^{23}_{577}$ −32.2, $[\alpha]^{23}_{546}$ −35.7 (*c* 3.1, $CDCl_3$); HRMS (FAB) *m*/*z* 330.1820 (MH, 330.1818 calcd for $C_{18}H_{24}O_3N_3$).

(4a*S*,7*S*)-1-(4-Bromobenzoylimino)-7-[2-(4-bromobenzoyloxy)ethyl]-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic Acid Benzyl Ester (24). 4-Bromobenzoyl chloride (400 mg, 1.81 mmol) was added at 0 °C to a solution of **23** (220 mg, 0.60 mmol), Et_3N (0.50 mL, 3.6 mmol), CH_2Cl_2 (10 mL), and a crystal of 4-(dimethylamino)pyridine. After 1 h, the reaction was partitioned between Et_2O (50 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated, the organic layer was washed with brine (10 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated. The residue was purified on silica gel (4:1 hexanes−EtOAc) to provide 150 mg (36%) of **24** as a colorless solid: mp 175−176 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 2H) 7.88 (d, J = 7.8 Hz, 2H) 7.56 (d, J = 7.8 Hz, 2H) 7.37−7.40 (m, 5H) 7.31 (d, J = 7.8 Hz, 2H) 5.15−5.25 (m, 2H) 4.79−4.82 (m, 1H) 4.52−4.53 (m, 2H) 4.41−4.45 (m, 1H) 2.56−2.61 (m, 1H) 2.48−2.53 (m, 1H) 2.31 (s, 3H) 2.13−2.19 (m, 1H) 1.92−1.96 (m, 1H) 1.56−1.73 (m, 2H), the NH signal was too broad to observe; ^{13}C NMR (125 MHz, $CDCl_3$) 176.9, 165.7, 165.4, 152.7, 143.7, 136.8, 135.8, 131.8, 131.0, 131.0,130.6, 128.9, 128.6, 128.3, 128.3, 128.2, 126.4, 101.0, 66.1, 62.3, 56.0, 55.9, 34.7, 33.7, 27.4, 18.9 ppm; IR (film) 1716, 1608 cm^{-1}; $[\alpha]^{23}_{D}$ −3.3, $[\alpha]^{23}_{577}$ −2.8, $[\alpha]^{23}_{546}$ −1.0, $[\alpha]^{23}_{435}$ +32.5, $[\alpha]^{23}_{405}$ +68.5, (*c* 1.75, $CHCl_3$). Anal. Calcd for $C_{32}H_{29}Br_2N_3O_5$: C, 55.27; H, 4.20; N, 6.04. Found: C, 55.20; H, 4.16; N, 6.04.

(*S*)-*N*-[(Aminomethylene)-4-methoxy-2,3,6-trimethylbenzenesulfonamide]-3-amino-7-methyl-6-octenol (25a). A solution of (*S*)-3-amino-7-methyl-6-octenol[4] (**19**, 1.00 g, 6.36 mmol), *S*,*S*,-dimethyl *N*--(4-methoxy-2,3,6-trimethylbenzenesulfonyl)-carbonimidodithioate (1.78 g, 5.34 mmol), and benzene (6 mL) was maintained at reflux for 2 h. The reaction was quenched by adding Et_2O (50 mL) and 0.1 M HCl (5 mL). The layers were separated, the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The resulting crude oil was purified by MPLC (1:1 hexanes−EtOAc) to provide 1.81 g (77%) of the corresponding pseudothiourea as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 9.8 Hz, 1H) 6.40 (s, 1H) 5.04−5.06 (m, 1H) 3.85 (s, 3H) 3.77−3.84 (m, 1H) 3.66−3.73 (m, 2H) 2.72 (s, 3H) 2.64 (s, 3H) 2.36 (s, 3H) 2.15 (s, 3H) 1.96−2.02 (m, 2H) 1.84−1.92 (m, 2H) 1.69 (m, 3H) 1.60−1.68 (m, 2H) 1.56 (m, 3H), the OH signal was too broad to observe; ^{13}C NMR (125 MHz, $CDCl_3$) 167.4, 158.8, 138.8, 137.0, 132.8, 132.4, 124.9, 122.7, 111.6, 58.7, 55.4, 52.2, 37.7, 35.4, 25.7, 24.1, 24.0, 18.4, 17.6, 14.2, 11.8 ppm; IR (film) 3480, 3290 cm^{-1}; $[\alpha]^{23}_{D}$ −15.3, $[\alpha]^{23}_{577}$ −14.7, $[\alpha]^{23}_{546}$ −17.9, $[\alpha]^{23}_{435}$ −31.8, $[\alpha]^{23}_{405}$ −39.2 (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{34}N_2O_4S_2$: C, 56.98; H, 7.74; N, 6.33. Found: C, 56.90; H, 7.69; N, 6.34.

Silver nitrate (26 mL, 0.2 M in MeCN) was added dropwise to a 0 °C solution of a 1.59 g (3.60 mmol) portion of this pseudothiourea and MeCN (75 mL) that had been saturated with NH_3.[17] The reaction mixture was allowed to warm to room temperature, and after 18 h, EtOAc (100 mL) was added and the resulting mixture was filtered through a plug of Celite. The eluent was concentrated to provide 1.46 g (99%) of **25a** as a colorless solid: mp 107−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (s, 2H) 6.15 (s, 1H) 4.90 (app s, 1H) 4.36 (s, 1H) 3.80 (app s, 4H) 3.53−3.66 (m, 3H) 2.64 (s, 3H) 2.56 (s, 3H) 2.10 (s, 3H) 1.85−1.86 (m, 2H) 1.71 (m, 1H) 1.56 (m, 3H) 1.39−1.32 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.5, 156.8, 138.3, 136.6, 132.9, 131.9, 124.8, 123.2, 111.7, 58.1, 55.3, 47.5, 38.4, 35.3, 25.5, 24.5, 24.1, 18.2, 17.4, 11.9 ppm; IR (film) 3442, 3354, 1621 cm^{-1}; $[\alpha]^{23}_{D}$ −20.0, $[\alpha]^{23}_{577}$ −20.7, $[\alpha]^{23}_{546}$ −23.0, $[\alpha]^{23}_{435}$ −33.2, $[\alpha]^{23}_{405}$ −35.7 (*c* 2.4, $CHCl_3$). Anal.

Calcd for $C_{20}H_{33}N_3O_4S$: C, 58.37; H, 8.08; N, 10.21. Found: C, 58.31; H, 8.05; N, 10.21.

(*S*)-*N*-[(Aminomethylene)-4-methoxy-2,3,6-trimethylbenzenesulfonamide]-3-amino-1-benzyloxy-7-methyl-6-octene (25b). Following the procedure described for preparing **25a**, **13** (0.807 g, 3.262 mmol) was converted in 80% overall yield to **25b**: a colorless oil; ^{1}H NMR (500 MHz, DMSO, 80 °C) δ 7.25−7.32 (m, 5H) 6.65 (s, 1H) 6.45 (s, 1H) 6.42 (s, 1H) 5.01 (m, 1H) 4.35 (s, 2H) 3.77 (s, 3H) 3.73 (m, 1H) 3.38−3.41 (m, 2H) 3.09 (s, 3H) 2.63 (s, 3H) 2.56 (s, 3H) 1.88 (m, 2H) 1.69 (m, 1H) 1.60 (m, 4H) 1.49 (s, 3H) 1.36−1.42 (m, 2H); ^{13}C NMR (125 MHz, DMSO, 80 °C) 157.3, 155.6, 138.2, 137.2, 135.3, 134.8, 130.5, 127.7, 126.9, 126.8, 123.4, 123.2, 111.6, 71.6, 66.5, 55.1, 47.5, 34.3, 34.2, 24.8, 23.5, 22.8, 17.4, 16.9, 11.2 ppm; IR (film) 3445, 3336, 1622, 1538 cm^{-1}; $[\alpha]^{23}_D$ +14.6, $[\alpha]^{23}_{577}$ +15.3, $[\alpha]^{23}_{546}$ +18.2, $[\alpha]^{23}_{435}$ +37.4, $[\alpha]^{23}_{405}$ +48.9 (*c* 1.80, $CHCl_3$). Anal. Calcd for $C_{27}H_{39}N_3O_4S$: C, 64.64; H, 7.84; N, 8.38. Found: C, 64.77; H, 7.88; N, 8.32.

Conversion of 25a to 27c and 28c under Knoevenagel Biginelli Conditions. Following the represenative olefin dihydroxylation and 1,2-diol cleavage procedure, **25a** (100 mg, 0.24 mmol) was converted to **26a**. Aminal **26a** was then condensed with **16** following the representative procedure for Biginelli condensation under Knoevenagel conditions with the exception that the concentration of **26a** in 2,2,2-trifluoroethanol was 0.5 M. Purification of the crude product on silica gel (1:1 hexanes−EtOAc) provided 80 mg (61%) of a 6:1 mixture of **27a** and **28a**.

A 120 mg (0.22 mmol) sample of a comparable product was esterified with 4-bromobenzoyl chloride (160 mg, 0.72 mmol) following the procedure described for the preparation of **24** to provide a crude residue that was purified on silica gel (3:1 hexanes−EtOAc) to provide 160 mg (100%) of a 6:1 mixture **27c** and **28c**. These isomers were separated by HPLC (6:1 hexanes−EtOAc; 20 mL/min, 300 × 22 mm 10 μm silica Alltech column) to give pure samples of **27c** (t_R = 62 min) and **28c** t_R = 53 min).

(4a*R*,7*S*)-7-[2-(4-Bromobenzoyloxy)ethyl]-1-(4-methoxy-2,3,6-trimethylbenzenesulfonylimino)-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (27c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H) 7.76 (d, *J* = 8.4 Hz, 2H) 7.51 (d, *J* = 8.4 Hz, 2H) 7.32−7.39 (m, 5H) 6.48 (s, 1H) 5.12−5.21 (m, 2H) 4.20−4.29 (m, 2H) 4.13−4.18 (m, 1H) 4.05−4.09 (m, 1H) 3.78 (s, 3H) 2.66 (s, 3H) 2.59 (s, 3H) 2.46−2.55 (m, 1H) 2.34 (s, 3H) 2.13−2.19 (m, 1H) 2.06 (s, 3H) 1.93−2.00 (m, 1H) 1.75−1.87 (m, 2H) 1.64−1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.5, 164.9, 158.5, 148.1, 145.6, 138.4, 136.5, 135.6, 132.9, 131.6, 131.0, 128.7, 128.6, 128.4, 128.3, 128.0, 124.7, 111.6, 103.8, 66.3, 62.4, 57.0, 55.3, 54.9, 32.5, 30.0, 28.5, 24.1, 18.5, 18.3, 11.8 ppm; IR (film) 3292, 1716, 1614 cm^{-1}; $[\alpha]^{23}_D$ +55.5, $[\alpha]^{23}_{577}$ +57.7, $[\alpha]^{23}_{546}$ +66.5, $[\alpha]^{23}_{435}$ +121, $[\alpha]^{23}_{405}$ +150 (*c* 2.1, $CHCl_3$). Anal. Calcd for $C_{35}H_{38}BrN_3O_7S$: C, 58.01; H, 5.29; N, 5.80. Found: C, 57.98; H, 5.42; N, 5.52.

(4a*S*,7*S*)-7-[2-(4-Bromobenzoyloxy)ethyl]-1-(4-methoxy-2,3,6-trimethylbenzenesulfonylimino)-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (28c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H) 7.76 (d, *J* = 8.4 Hz, 2H) 7.51 (d, *J* = 8.4 Hz, 2H) 7.33−7.54 (m, 5H) 6.44 (s, 1H) 5.12−5.23 (m, 2H) 4.36−4.44 (m, 2H) 4.27−4.29 (m, 2H) 3.80 (s, 3H) 2.65 (s, 3H) 2.56 (s, 3H) 2.46−2.51 (m, 1H) 2.29 (s, 3H) 2.02−2.10 (m, 4H) 1.75−1.82 (m, 1H) 1.48−1.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.6, 165.3, 158.5, 146.7, 143.0, 138.4, 136.9, 135.8, 133.0, 131.6, 131.0, 128.7, 128.6, 128.3, 128.2, 128.0, 124.8, 111.6, 100.6, 66.2, 62.0, 56.2, 56.1, 55.4, 34.5, 33.2, 27.7, 24.0, 18.9, 18.3, 11.8 ppm; IR (film) 3298, 1716, 1614 cm^{-1}; $[\alpha]^{23}_D$ −17.7, $[\alpha]^{23}_{577}$ −16.1, $[\alpha]^{23}_{546}$ −18.3, $[\alpha]^{23}_{435}$ −19.4, $[\alpha]^{23}_{405}$ −13.3 (*c* 0.75, $CHCl_3$). Anal. Calcd for $C_{35}H_{38}BrN_3O_7S$: C, 58.01; H, 5.29; N, 5.80. Found: C, 58.06; H, 5.41; N, 5.55.

Conversion of 25b to 27b and 28b under Knoevenagel Biginelli Conditions. Following the represenative olefin dihydroxylation and 1,2-diol cleavage procedure, **25b** (100 mg, 0.20 mmol) was converted to **26b**, and this crude material was condensed with **16** following the representative procedure for Biginelli condensation under Knoevenagel conditions with the exception that the concentration of **26b** in 2,2,2-trifluoroethanol was 0.5 M. Purification of the crude product on silica gel (4:1 hexanes−EtOAc to 2:1 hexanes−EtOAc) provided 106 mg (84%) of a 7:1 mixture of **27b** and **28b**. Characterization data for the major product (4a*R*,7*S*)-7-(2-Benzyloxyethyl)-1-(4-methoxy-2,3,6-trimethylbenzenesulfonylimino)-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid benzyl ester (**27b**) as determined from this mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H) 7.23−7.42 (m, 10H) 6.52 (s, 1H) 5.15−5.25 (m, 2H) 4.28−4.36 (m, 2H) 4.23 (d, *J* = 11.1, 4.0 Hz, 1H) 4.03−4.07 (m, 1H) 3.82 (m, 3H) 3.40−3.42 (m, 2H) 2.70 (s, 3H) 2.62 (s, 3H) 2.48−2.50 (m, 1H) 2.31 (s, 3H) 2.13 (s, 3H) 2.00−2.05 (m, 1H) 1.93−1.95 (m, 2H) 1.79−1.83 (m, 1H) 1.47−1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.1, 158.5, 148.1, 145.6, 138.5, 138.2, 136.4, 135.7, 133.2, 128.6, 128.4, 128.2, 128.2, 127.5, 127.4, 124.7, 111.7, 103.9, 72.5, 67.7, 66.3, 57.0, 55.9, 55.3, 33.4, 30.0, 28.8, 24.0, 18.5, 18.3, 11.9 ppm; IR (film) 3289, 1704, 1614 cm^{-1}. Anal. Calcd for $C_{35}H_{41}N_3O_6S$: C, 66.54; H, 6.54; N, 6.65. Found: C, 66.66; H, 6.57; N, 6.66.

Conversion of 25b to (4a*S*,7*S*)-7-(2-Benzyloxyethyl)-1-(4-methoxy-2,3,6-trimethylbenzenesulfonylimino)-3-methyl-1,2,4a,5,6,7-hexahydropyrrolo-[1,2-*c*]pyrimidine-4-carboxylic Acid Benzyl Ester (28b) by Biginelli Condensation in the Presence of PPE. Following the representative procedure for olefin dihydroxylation and 1,2-diol cleavage, **25b** (100 mg, 0.20 mmol) was converted to **26b**. Crude aminal **26b** was then condensed with **16** following the representative procedure for Biginelli condensation in the presence of PPE to give, after purification on silica gel (2:1 hexanes−EtOAc to 1:1 hexanes−EtOAc), 77 mg (61%) of **28b**, which was contaminated with a trace of **27b** (3%). **28b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H) 7.22−7.42 (m, 10H) 6.54 (s, 1H) 5.16−5.26 (m, 2H) 4.36−4.40 (m, 2H) 4.26−4.35 (m, 2H) 3.84 (m, 3H) 3.45−3.48 (m, 2H) 2.72 (s, 3H) 2.65 (s, 3H) 2.45−2.50 (m, 1H) 2.32 (s, 3H) 2.15−2.20 (m, 1H) 2.14 (s, 3H) 2.00−2.05 (m, 1H) 1.62−1.72 (m, 1H) 1.51−1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 158.5, 146.4, 142.9, 138.6, 136.4, 135.8, 133.4, 128.6, 128.3, 128.2 128.2, 127.5, 127.4, 127.4, 124.7, 111.6, 100.5, 72.5, 67.2, 66.1, 56.4, 56.0, 55.3, 34.5, 34.1, 27.7, 24.0, 18.8, 18.3, 11.9 ppm; IR (film) 3290, 1712, 1614 cm^{-1}; $[\alpha]^{23}_D$ −65.8, $[\alpha]^{23}_{577}$ −67.5, $[\alpha]^{23}_{546}$ −76.7, $[\alpha]^{23}_{435}$ −117, $[\alpha]^{23}_{405}$ −128 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{35}H_{41}N_3O_6S$: C, 66.54; H, 6.54; N, 6.65. Found: C, 66.49; H, 6.51; N, 6.56.

Conversion of 28c to 24. A solution of **28c** (15 mg, 20 mmol) and TFA (2 mL) was maintained for 1 h at room temperature. The reaction was concentrated, and the resulting crude was oil used without purification. 4-Bro-

mobenzoyl chloride (22 mg, 0.10 mmol) was added to a 0 °C solution of this crude guanidine, Et_3N (0.15 mL, 1.08 mmol), CH_2Cl_2 (2 mL) and a crystal of 4-(dimethylamino)-pyridine. After 1 h, the reaction was quenched with Et_2O (10 mL) and saturated aqueous NH_4Cl (2 mL). The layers were separated, the organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The residue was purified on silica gel (4:1 hexanes−EtOAc) to provide 4 mg (29%) of **24** as a colorless solid.

***S,S*-Dimethyl *N*-(4-Methoxy-2,3,6-trimethylbenzenesulfonyl)carbonimidodithioate.** Ammonia was bubbled through a solution of 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride[27] (10.3 g, 43.6 mmol) and CH_2Cl_2 (100 mL) at 0 °C. After 30 min, acetone (0.5 L) was added, and the reaction mixture was filtered through a plug of silica gel and concentrated. The resulting solid was trituated with Et_2O to provide 9.18 g (92%) of 4-methoxy-2,3,6-trimethylbenzenesulfonamide as a colorless solid: mp 175−176 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 6.75 (s, 1H) 6.36 (s, 2H) 3.86 (s, 3H) 2.63 (s, 3H) 2.58 (s, 3H) 2.05 (s, 3H); ^{13}C NMR (100 MHz, acetone-d^6) 159.7, 139.0, 138.0, 134.6, 125.3, 113.0, 56.2, 24.4, 18.5, 12.3 ppm; IR (KBr) 3385, 3279, 2983, 2942, 1582, 1560, 1486, 1309, 1148, 1113 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.46; H, 6.55; N, 6.05.

A solution of of 4-methoxy-2,3,6-trimethylbenzenesulfonamide (9.15 g, 39.9 mmol) and DMF (50 mL) was added to a mixture of NaH (4.11 g, 98.6 mmol, washed 3× with hexanes) and DMF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred vigorously for 10 min before CS_2 (6.9 mL, 11 mmol) was added. After another 10 min, MeI (7.85 mL, 126 mmol) was added. After another 15 min, the reaction was poured into saturated aqueous NH_4Cl (200 mL) and extracted with $CHCl_3$ (3 × 0.5 L). The combined organic layers were dried ($MgSO_4$), filtered through a plug of silica gel, and concentrated. The crude solid was trituated with MeOH to provide 11.1 g (84%) of *S,S*-dimethyl *N*-(4-methoxy-2,3,6-trimethylbenzenesulfonyl)carbonimidodithioate as a colorless solid: mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H) 3.84 (s, 3H) 2.71 (s, 3H) 2.57 (s, 3H) 2.52 (s, 6H) 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 182.3, 159.3, 139.2, 138.5, 130.3, 125.0, 111.7, 55.4, 23.9, 18.5, 16.3, 11.9 ppm; IR (film) 2969, 2930, 1552, 1476, 1386, 1307, 1146, 997, 925, 804 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_3S_3$: C, 46.82; H, 5.74; N, 4.20. Found: C, 46.82; H, 5.73; N, 4.22.

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Supporting Information Available: Copies of ^{13}C NMR spectra of **1a**, **15**, **22**, **26a**, and **26b** and copies of ^{1}H NMR and ^{13}C NMR spectra of **17a**, **18a**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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