JOC*Article*

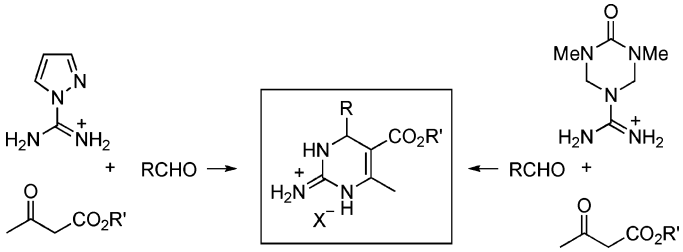
Concise Synthesis of Guanidine-Containing Heterocycles Using the Biginelli Reaction

Bradley L. Nilsson and Larry E. Overman*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

leoverma@uci.edu

Received June 9, 2006



Two general methods for the synthesis of 2-imino-5-carboxy-3,4-dihydropyrimidines were developed using the three-component Biginelli reaction. The first method utilizes pyrazole carboxamidine, a β-ketoester, and an aldehyde in an initial Biginelli reaction. After Boc protection, these products undergo aminolysis and acidic deprotection to generate 2-imino-5-carboxy-3,4-dihydropyrimidines in a four-step sequence. The second method utilizes a triazone-protected guanidine, a β-ketoester, and an aldehyde in a Biginelli reaction. Acidic cleavage of the triazone yields 2-imino-5-carboxy-3,4-dihydropyrimidines in a two-step sequence. We also describe the further elaboration of several of these products using a tethered Biginelli reaction to give triazaacenaphthalene structures similar to those found in crambescidin and batzelladine alkaloids.

Introduction

Guanidine functional groups are found in numerous biologically active natural products and several drugs and drug candidates.[1,2] These guanidine-containing therapeutics include cardiovascular, antihistamine, anti-inflammatory, antidiabetic, antibacterial, antiviral, and antineoplastic drugs.[1] The diversity in activity of these compounds likely derives, in part, from the ability of guanidinium cations to recognize receptors by a variety of noncovalent interactions, including hydrogen-bonding, electrostatic, and π-stacking associations.[3]

Various natural products contain the guanidine functional group embedded in a six-membered ring, such as the Na^+ channel blocker saxitoxin (**1**), the puffer fish poison tetrodotoxin (**2**), and the nucleoside base guanine. There are several structurally novel marine alkaloids that contain a guanidine unit within complex polycyclic architectures. These include the crambescidin[4] (examples **3**−**5**) and batzelladine[4i,5] (**6**) families, which are related by their triazaacenaphthalene core structures. These guanidine alkaloids, and some of their synthetic derivatives, display promising anticancer[4a−h,k,6] and antiviral activities.[4b−d,h,j,6c] They have also been shown to inhibit important protein−protein

(1) Greenhill, J. V.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203−326.

(2) For reviews of guanidine-containing natural products, see: (a) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516−550. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617−649. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198. (d) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (e) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377−409.

(3) Arndt, H.-D.; Koert, U. *Organic Synthesis Highlights IV* **2000**, 241−250 and references contained therein.

(4) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925−8926. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8372−8479. (c) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712−5715. (d) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805−4808. (e) Rinehart, K. L.; Jares-Erijman, E. A. U.S. Patent 5,756,734, 1998. (f) Shi, J.-G.; Sun, F.; Rinehart, K. L. WO Patent 3,756,734, 1998. (g) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007−1015. (h) Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carré, J. B.; Debitus, C.; Lucarain, L.; Provost, J. *Tetrahedron* **1995**, *51*, 3675−3682. (i) Braekman, J. C.; Daloze, D.; Tavares, R.; Hajdu, E.; Van Soest, R. W. M. *J. Nat. Prod.* **2000**, *63*, 193−196. (j) Chang, L. C.; Whittaker, N. F.; Bewley, C. A. *J. Nat. Prod.* **2003**, *66*, 1490−1494. (k) Aoki, S.; Kong, D.; Matsui, K.; Kobayashi, M. *Anticancer Res.* **2004**, *24*, 2325−2330.

10.1021/jo061199m CCC: $33.50
Published on Web 08/26/2006

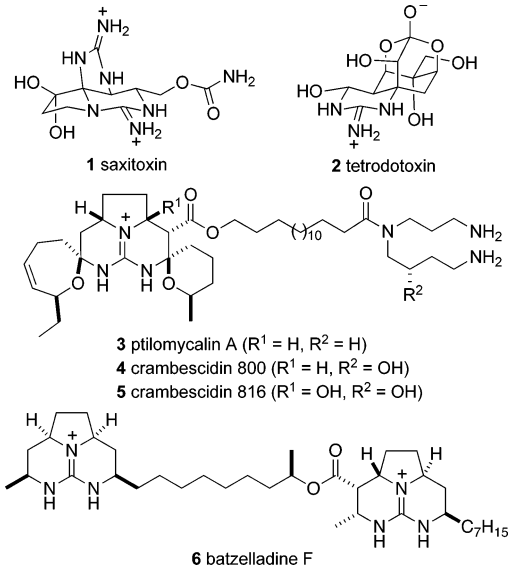


FIGURE 1.

interactions,[4g,5a,b,7] voltage-sensitive Ca^{2+} channels,[4j] and Na^+, K^+, and Ca^{2+} ATPases.[8] The complex architecture of the crambescidins and the batzelladines and their compelling biological activities have sparked intense effort toward their total chemical synthesis.[9] Notably, the Snider[10] and Murphy[11] groups developed biomimetic approaches, the Nagasawa[12] group used a 1,3-dipolar cycloaddition approach, and the Overman[13] group pioneered the use of tethered Biginelli[9b,14] reactions for assembly of crambescidin alkaloids. The batzelladines and their analogues have also attracted considerable synthetic attention from the Overman,[15] Snider,[16] Murphy,[17] and Nagasawa[18] groups, among others.[19]

The existing chemistry for the synthesis of complex guanidine natural products of the crambescidin and batzelladine families and their analogues, although highly refined, requires many steps. We have, therefore, directed some effort to the development of new chemistry that will allow access to analogues of these guanidine-containing compounds in just a few steps. The Biginelli reaction[20] utilizes urea, an aldehyde, and a β-ketoester in a three-component condensation giving rise to dihydropyrimidinone products.[14] The related condensation of guanidine, an aldehyde, and a β-ketoester to form six-membered guanidine-containing heterocycles, 2-imino-5-carboxy-3,4-dihydropyrimidines **10**, (eq 1) is much less well developed.[14,21] Cho[21a] and Atwal[21b] both demonstrated that reactions between the Knoevenagel product of ethyl acetoacetate and 3-nitrobenzaldehyde with guanidine or methylguanidine give Biginelli adducts, albeit in low yields (14−25%). Milcent showed that yields are improved when the R^1 substituent of the β-ketoester is phenyl rather than methyl (eq 2).[21c] In these latter examples, double Biginelli adducts **12** are also observed as byproducts when guanidine is used. Kappe also showed that guanidine can be successfully used in a traditional three-component Biginelli reaction when the β-ketoester possesses a phenyl substituent (as in the case of ethyl benzoyl acetate, R^1 = Ph) to give Biginelli adducts in satisfactory yields while avoiding double Biginelli byproducts.[21d] Finally, multistep Biginelli−aminolysis strategies in which isoureas or isothioureas are used as guanidine precursors to access 2-imino-3,4-dihydropyrimidines are precedented in the literature.[22] For example, Atwal demonstrated the aminolysis of Biginelli adducts containing methyl isourea[22a]

(5) (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, 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*, 1182−1188. (b) Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carté, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1997**, *62*, 1814−1819.

(6) (a) Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K. *Tetrahedron Lett.* **2003**, *44*, 251−254. (b) Black, G. P.; Coles, S. J.; Hizi, A.; Howard-Jones, A. G.; Hursthouse, M. B.; McGown, A. T.; Loya, S.; Moore, C. G.; Murphy, P. J.; Smith, N. K.; Walshe, N. D. *Tetrahedron Lett.* **2001**, *42*, 3377−3381. (c) Aron, Z. D.; Pietraszkiewicz, H.; Overman, L. E.; Valeriote, F.; Cuevas, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3445−3449.

(7) (a) Olszewski, A.; Sato, K.; Aron, Z. D.; Cohen, F.; Harris, A.; McDougall, B. R.; Robinson, W. E., Jr.; Overman, L. E.; Weiss, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 14079−14084. (b) Olszewski, A.; Weiss, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 12178−12179.

(8) (a) Ohizumi, Y.; Sasaki, S.; Kusumi, T.; Ohtani, I. I. *Eur. J. Pharmacol.* **1996**, *310*, 95−98. (b) Georgieva, A.; Hirai, M.; Hashimoto, Y.; Nakata, T.; Ohizumi, Y.; Nagasawa, K. *Synthesis* **2003**, 1427−1432.

(9) For brief reviews of the synthesis and isolation of crambescidins, see: (a) Reference 2b. (b) Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, 253−265. (c) Heys, L.; Moore, C. G.; Murphy, P. *J. Chem. Soc. Rev.* **2000**, *29*, 57−67.

(10) (a) Snider, B. B.; Shi, Z. *Tetrahedron Lett.* **1993**, *34*, 2099−2102. (b) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549−557.

(11) (a) Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Abdul Malik, K. M. *J. Chem. Soc., Chem. Commun.* **1994**, 119−120. (b) Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron* **1996**, *52*, 8315−8332. (c) Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, A. K. *Tetrahedron Lett.* **2003**, *44*, 251−254.

(12) (a) Nagasawa, K.; Georgieva, A.; Nakata, T. *Tetrahedron* **2000**, *56*, 187−192. (b) Nagasawa, K.; Georgieva, A.; Nakata, T.; Kita, T.; Hasimoto, Y. *Org. Lett.* **2002**, *4*, 177−180.

(13) (a) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235−3237. (b) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657−2658. (c) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **1999**, *121*, 6944−6945. (d) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893−4903. (e) Coffey, D. S.; Overman, L. E.; Stappenbeck, F. *J. Am. Chem. Soc.* **2000**, *122*, 4904−4914. (f) Aron, Z. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 3380−3390. (g) Rhee, Y. H.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 15652−15658.

(14) For a comprehensive review of the Biginelli reaction, see: Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1−116.

(15) (a) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512−1519. (b) Cohen, F.; Overman, L. E.; Sakata, S. K. L. *Org. Lett.* **1999**, *1*, 2169−2172. (c) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 10782−10783. (d) Cohen, F.; Collins, S. K.; Overman, L. E. *Org. Lett.* **2003**, *5*, 4485−4488. (e) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594−2603. (f) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2604−2608.

(16) (a) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980. (b) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697−5700.

(17) (a) See ref 11a. (b) Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron Lett.* **1996**, *37*, 6043−6046. (c) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481−9488. (d) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554.

(18) (a) Nagasawa, K.; Koshino, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 4155−4158. (b) Ishiwata, T.; Hino, T.; Koshino, H.; Hasimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett.* **2002**, *4*, 2921−2924.

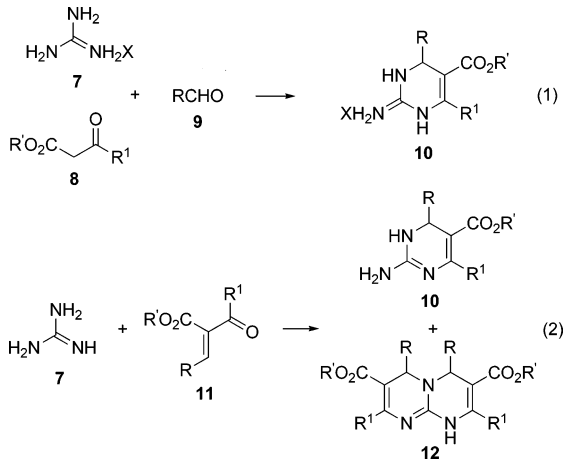
(19) (a) Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905−908. (b) Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551−1554.

(20) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.

(21) (a) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. *J. Org. Chem.* **1985**, *50*, 4227−4230. (b) Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem.* **1990**, *33*, 1510−1515. (c) Milcent, R.; Malanda, J.-C.; Barbier, G. *J. Heterocycl. Chem.* **1997**, *34*, 329−336. (d) Vanden Eynde, J. J.; Hecq, N.; Kataeva, O.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 1785−1791.

(22) (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898−5907. (b) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49−51.

fragments, whereas Kappe prepared 2-imino-3,4-dihydropyrimidine salts by aminolysis of resin-bound isothiourea Biginelli adducts.[22b]

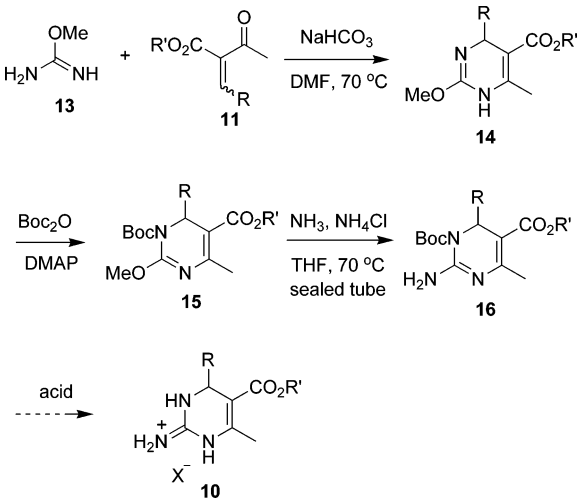


In the course of our efforts to prepare focused libraries of polycyclic guanidines, we discovered that direct three-component Biginelli reactions with guanidine are useful only with benzoyl acetates and aryl aldehydes. Attempted reactions using acetoacetates (R^1 = Me) failed to give useful yields of the desired Biginelli adducts. We thus undertook the development of more general Biginelli-based methods for preparing 2-imino-5-carboxy-3,4-dihydropyrimidines.

Results

Synthesis of 2-Imino-5-carboxy-3,4-dihydropyrimidines: Aminolysis Strategy. Our initial efforts focused on Biginelli reactions with guanidine surrogates followed by aminolysis of the resulting products (Scheme 1). Atwal-type Biginelli reactions

SCHEME 1



with *O*-methylisourea **13** and Knoevenagel precursors **11** to give dihydropyrimidines **14** are well established.[23] However, aminolysis of these methoxy-1,4-dihydropyrimidines proved to be problematic in our hands. Specifically, it was found that direct aminolysis of methoxydihydropyrimidines **14** was prohibitively sluggish. We hoped that installation of an acyloxy group at N3

(23) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185−1188.

SCHEME 2

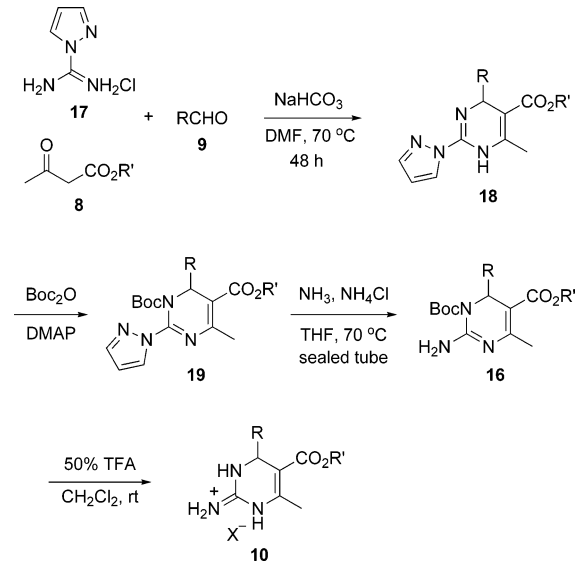


TABLE 1. Synthesis of Biginelli Adducts 18 Using Pyrazole Carboxamidine Hydrochloride 17

entry	R′	R	product	yield (%)
1	Et	Ph	**18a**	73
2	Et	*o*-vinyl−C_6H_4	**18b**	58
3	Bn	*i*-Pr	**18c**	74
4	Bn	*n*-Pr	**18d**	65
5	Bn	cyclohexyl	**18e**	63
6	Et	*m*-NO_2−C_6H_4	**18f**	60

to give substrates of type **15** would improve aminolysis rates, similar to effects reported by Atwal.[22a] However, <10% conversion of Boc-protected methoxydihydropyrimidines **15** to aminolysis products **16** was observed, even after 45 h at 70 °C.

In an attempt to identify Biginelli products in which subsequent aminolysis to generate a guanidine functional group would be more facile, pyrazole carboxamidine hydrochloride (**17**) was chosen as a coupling partner for Biginelli condensations (Scheme 2). It was reasoned that Biginelli adducts **18** would be efficient substrates for aminolysis based on the common use of **17** as a guanylating agent.[24] The initial Biginelli condensation in this sequence when carried out in DMF at 70 °C proceeded in moderate to good yields (58−73%, Table 1). Reaction times of 48 h were required, as the final dehydration step to form the $\Delta^{5,6}$ alkene was slow relative to the comparable step in Biginelli reactions employing urea. Both aromatic and aliphatic aldehydes could be effectively used as reaction substrates. However, three of the representative aldehydes we examined did not give rise to the desired products: 2-furaldehyde and pivaldehyde failed to give isolable Biginelli adducts, whereas *p*-nitrobenzaldehyde provided marginal yields of Biginelli products as part of intractable mixtures. Biginelli products **18** are depicted in Scheme 2 as the $\Delta^{2,3}$ tautomers; however, NMR analysis shows that these heterocycles are mixtures of the $\Delta^{2,3}$ and the $\Delta^{1,2}$ tautomers in variable ratios.

We initially examined direct aminolysis of Biginelli adducts **18** using the conditions described by Atwal[22a] for related methyl isourea adducts. These Biginelli products were dissolved in THF,

(24) (a) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497−2502. (b) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389−3392.

TABLE 2. Conversion of Pyrazole Biginelli Adducts 18 to Guanidines 10 by the Sequence Depicted in Scheme 2

entry	R′	R	product	yield (%)	product	yield (%)	product	yield (%)
1	Et	Ph	**19a**	67	**16a**	77	**10a**	90
2	Et	*o*-vinyl−C_6H_4	**19b**	86	**16b**	60	**10b**	65
3	Bn	*i*-Pr	**19c**	68	**16c**	63	**10c**	86
4	Bn	*n*-Pr	**19d**	99	**16d**	70	**10d**	68
5	Bn	cyclohexyl	**19e**	89	**16e**	86	**10e**	95
6	Et	*m*-NO_2−C_6H_4	**19f**	53	**16f**	75	**10f**	94

cooled to 0 °C, and saturated with ammonia by bubbling ammonia gas through the solution for 15 min. The resulting solution was then heated at 70 °C in a sealed tube. Direct aminolysis under these conditions was too slow to be practical. However, introduction of a Boc group significantly improved the rate of aminolysis. Substrates **18a**−**f** were Boc-protected using standard conditions (DMAP, Boc_2O) to give compounds **19a**−**f** in good yields (Table 2). These products exist as mixtures of tautomers, with the Boc substituent assumed to be at N3 based on precedent for related functionalizations of 2-methoxy- and 2-[[(4-methoxyphenyl)methyl]thio]-1,4-dihydropyrimidines.[22a] Substrates **19a**−**f** typically underwent aminolysis at 70 °C within 24 h to give good yields of Boc-protected guanidine products **16a**−**f** (Table 2).[25]

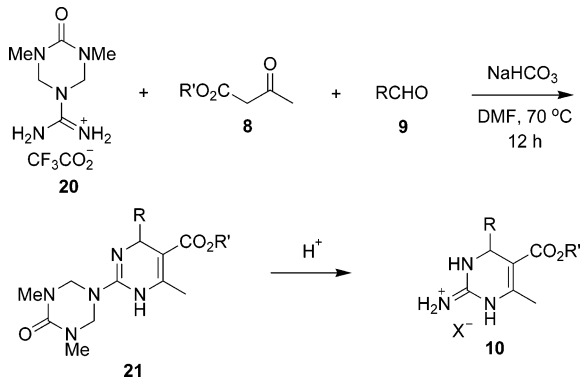
Removal of the Boc group from aminolysis products **16** was facile. Exposing compounds **16a**−**f** to 50% TFA in dichloromethane at room temperature for 1 h gave 2-imino-5-carboxy-3,4-dihydropyrimidines **10a**−**f** as their trifluoroacetate salts (Table 2). Recrystallization of these salts provided pure products in good to excellent yields.

The pyrazole Biginelli reaction−aminolysis sequence outlined in Scheme 2 provides a reasonably general method for preparing 2-imino-5-carboxy-3,4-dihydropyrimidines in four steps from a β-ketoester, an aldehyde, and a pyrazole carboxamidine hydrochloride (**17**). For the substrates examined, overall yields ranged from 19 to 46%. Of most significance, this strategy can be used with aliphatic as well as aromatic aldehydes and is not limited to the use of benzoyl acetates as the β-ketoester component.

Protected Guanidine Strategy. Although Biginelli reactions with guanidines containing a single alkyl substituent proceed in low to moderate yields,[21a−c] we postulated that *N*,*N*-dialkylguanidines might give improved yields in Biginelli condensations. Initial support for this supposition came from the Biginelli reaction of *N*,*N*-diallylguanidine,[26] benzaldehyde, and benzyl acetoacetate in sodium bicarbonate-buffered DMF, which gave the Biginelli adduct in 80% yield (70 °C, 11 h). However, preliminary attempts to remove the allyl protecting groups from the resulting product were not encouraging.

On the basis of this result, other substituted guanidines were surveyed in order to identify a protected guanidine that would both participate in Biginelli condensations and allow subsequent deprotection to be accomplished efficiently. Neither Boc-guanidine[27] nor *p*-tosylguanidine[28] were reactive in Biginelli condensations using numerous reaction conditions (acidic, basic, Lewis acidic).[14] The reduced basicity of these guanidines compared to *N*,*N*-diallylguanidine likely accounts for this lack of reactivity.[29] 1,3,5-Triaz-4-ones have been employed as masked primary amines.[30] We reasoned that the related triazone derivative **20** (Scheme 3) would more closely approximate the basicity and nucleophilicity of *N*,*N*-dialkylguanidines during Biginelli condensations to give products that potentially could be converted to simple guanidines under acidic conditions (Scheme 3).

SCHEME 3



The preparation of 3,5-dimethyl-4-oxo-[1,3,5]triazinane-1-carboxamidine (**20**) is summarized in Scheme 4. Benzylamine was first converted to triazone derivative **25** by standard condensation with *N*,*N*′-dimethylurea and aqueous formaldehyde. The benzyl group was subsequently removed by high-pressure hydrogenation to give 1,3-dimethyl-[1,3,5]triazinan-2-one (**26**) in 96% yield. Upon heating triazone **26** and *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**27**) at 70 °C in THF, the di-Boc-protected guanidine precursor **28** was formed in 53% yield (80% based on consumed starting material); extended reaction times or elevated temperatures gave rise to unwanted byproducts. The Boc-protecting groups of product **28** were easily removed by reaction with 50% TFA in dichloromethane at room temperature to give the triazone-protected guanidine **20** in quantitative yield.

Triazone-protected guanidine **20** performed well in three-component Biginelli condensations. Heating an aldehyde (aromatic or aliphatic), β-ketoester, and guanidine **20** at 70 °C for 12 h in sodium bicarbonate-buffered DMF gave good yields (62−86%) of Biginelli adducts **21a**−**j** (Table 3). These Biginelli condensations reached completion more quickly than the corresponding reactions of pyrazole carboxamidine **17**. In addition, 2-furaldehyde, pivaldehyde, and *p*-nitrobenzaldehyde were used successfully in Biginelli reactions with **20**.

(25) We initially included ammonium chloride (0.5 equiv) in the reaction mixture to serve as a proton source. Later, it was found that omitting ammonium chloride had no deleterious effect on the outcome of these aminolysis reactions.

(26) Schaefer, F. C.; Wright, A. C. U.S. Patent 3,734,939, 1973.

(27) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136.

(28) Qi, Y.; Gao, H.; Yang, M.; Xia, C.-G.; Suo, J. *Synth. Commun.* **2003**, *33*, 1073−1079.

(29) The pK_a of *N*,*N*′-dimethylguanidinium sulfate is 13.4 and that of carbamate-substituted guanidines is ∼7.0; the pK_a of *N*-tosylguanidines should be lower, pK_a ∼2.0. See: Taylor, P. J.; Wait, A. R. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1765−1770.

(30) (a) Knapp, S.; Hale, J. J.; Bastos, M.; Gibson, F. S. *Tetrahedron Lett.* **1990**, *31*, 2109−2112. (b) Knapp, S.; Hale, J. J.; Bastos, M.; Molina, A.; Chen, K. Y. *J. Org. Chem.* **1992**, *57*, 6239−6256. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.

SCHEME 4

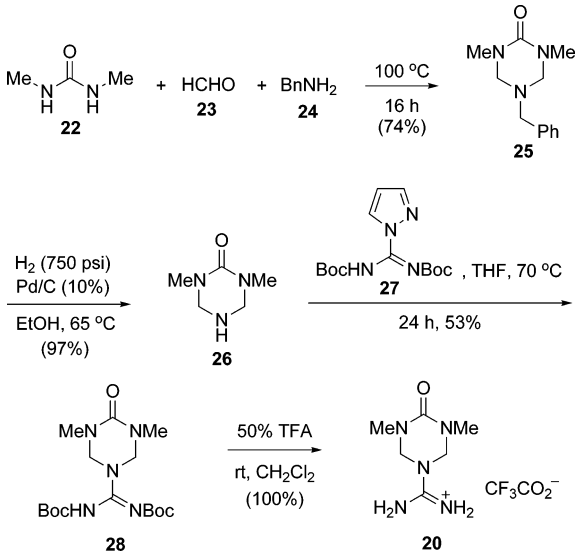
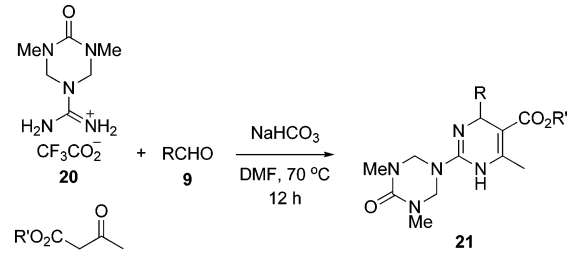


TABLE 3. Biginelli Reactions with Triazone-Protected Guanidine 20

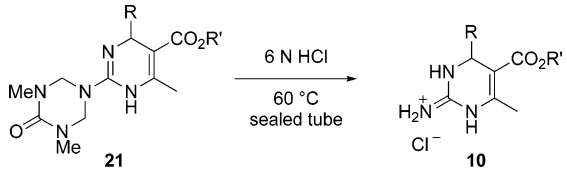


entry	R′	R	product	yield (%)
1	Et	Ph	**21a**	73
2	Et	*o*-vinyl−C_6H_4	**21b**	73
3	Bn	*i*-Pr	**21c**	86
4	Bn	*n*-Pr	**21d**	76
5	Bn	cyclohexyl	**21e**	91
6	Et	*m*-NO_2−C_6H_4	**21f**	71
7	Et	2-furanyl	**21g**	67
8	Bn	*t*-Bu	**21h**	43
9	Et	*p*-NO_2−C_6H_4	**21i**	86
10	Et	2,4-di-MeO−C_6H_4	**21j**	62

We turned to examine conditions for removal of the triazone group from compounds **21a**−**j** in order to reveal the unprotected guanidine functional group. Unfortunately, the triazone ring of these guanidines was not unraveled under the mildly acidic conditions previously used for cleaving triazone derivatives of alkylamines.[30b] For example, exposure of these products to 2−6 N HCl in EtOH at room temperature resulted in no deprotection after 16 h; various other acids gave similar results. Heating adducts **21a**−**j** in 6 N HCl in EtOH to 60 °C gave incomplete deprotection in the same time period. Finally, it was discovered that heating these substrates in 6 N aqueous HCl at 60 °C for 24 h in a sealed tube (to prevent loss of HCl) gave complete deprotection in most cases (Table 4). Not surprisingly, these relatively harsh acidic conditions were problematic with some substrates; compounds **21g**, **21h**, and **21j** underwent extensive decomposition under these conditions.

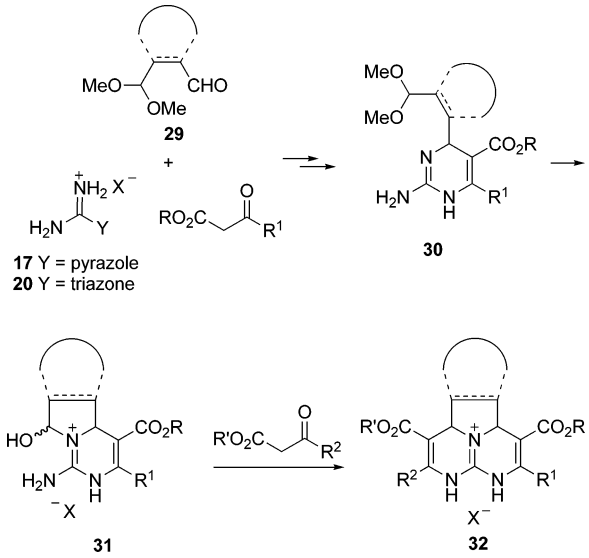
This triazone-protected guanidine Biginelli strategy provides 2-imino-5-carboxy-3,4-dihydropyrimidines in only two steps with good overall yields (53−76%). However, this sequence is limited to substrates that survive the strongly acidic conditions required to remove the triazone-protecting group from the Biginelli product.

TABLE 4. Deprotection of Triazone-Protected Biginelli Adducts



entry	R′	R	product	yield (%)
1	Et	Ph	**10a**	84
2	Et	*o*-vinyl−C_6H_4	**10b**	69
3	Bn	*i*-Pr	**10c**	84
4	Bn	*n*-Pr	**10d**	76
5	Bn	cyclohexyl	**10e**	83
6	Et	*m*-NO_2−C_6H_4	**10f**	84
7	Et	2-furan	**10g**	
8	Bn	*t*-Bu	**10h**	
9	Et	*p*-NO_2−C_6H_4	**10i**	79
10	Et	2,4-di-MeO−C_6H_4	**10j**	

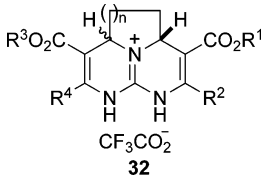
SCHEME 5



Transformation of 2-Imino-5-carboxy-3,4-dihydropyrimidinones Derived From Masked Dialdehydes to Hexahydrotriazaacenaphthalenes. With two methods for the preparation of 2-imino-5-carboxy-3,4-dihydropyrimidines in hand, we applied these procedures in the synthesis of hexahydrotriazaacenaphthalene structures, envisioning the use of a masked dialdehyde **29** (Scheme 5) in an initial Biginelli reaction to give 2-iminodihydropyrimidine products **30**. The protected aldehyde functional group would then be unmasked to generate pyrrolopyrimidinium hemiaminals of type **31**. These cyclic hemiaminals would finally be used in tethered Biginelli reactions[9b] with a second β-ketoester to give hexahydrotriazaacenaphthalenes **32**.

A variety of Boc-protected 2-imino-5-carboxy-3,4-dihydropyrimidines **30a**−**e** were synthesized from masked dialdehydes **29a**,**b**[31] using the pyrazole variant of our Biginelli−aminolysis strategy (Scheme 6). The initial Biginelli adducts **33a**−**e** were synthesized in yields ranging from 61 to 73%. These Biginelli condensations were successful with the monodimethyl acetal-protected dialdehydes **29a**,**b** and β-ketoesters having various

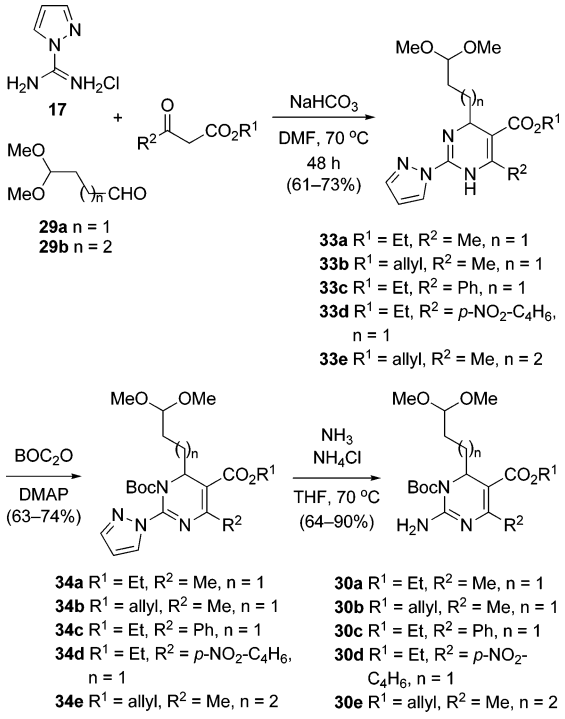
TABLE 5. Triazaacenaphthalene and Related Structures



32

entry	R^1	R^2	R^3	R^4	*n*	product	yield (%)	dr (*syn*:*anti*)
1	Et	Me	Me	Me	1	**32a**	70	3:1
2	Et	Ph	allyl	Me	1	**32b**	68	1:1.3
3	Et	Ph	Et	C_6F_5	1	**32c**	86	3.2:1
4	Et	*p*-NO_2−C_6H_4	allyl	Me	1	**32d**	90	1:1.3
5	Et	*p*-NO_2−C_6H_4	Bn	Me	1	**32e**	54	3.2:1
6	Et	*p*-NO_2−C_6H_4	allyl	$(CH_2)_4OBn$	1	**32f**	51	1:1
7	allyl	Me	Et	*p*-NO_2−Ph	2	**32g**	27	1:0

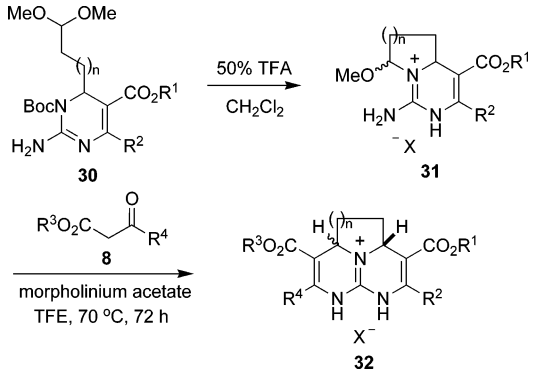
SCHEME 6



groups at R^1 (ethyl and allyl esters) and R^2 (methyl, phenyl, *p*-nitrophenyl). Boc protection and subsequent aminolysis of these Biginelli products proceeded in good yields to give products **30a**−**e**.

The Boc-protected 2-imino-5-carboxy-3,4-dihydropyrimidine products were converted to hexahydrotriazaacenaphthalenes as summarized in Scheme 7. Treatment of compounds **30a**−**e** with trifluoroacetic acid at room temperature resulted in cleavage of the Boc and dimethylacetal groups and ring closure to give tetrahydropyrrolopyrimidinium salts of type **31**. The solvent and excess TFA were removed from these products under reduced pressure; these crude intermediates were then redissolved in trifluoroethanol containing an excess of a second β-ketoester. These solutions were then heated in the presence of morpholinium acetate as a promoter and sodium sulfate as a desiccant to give hexahydrotriazaacenaphthalene tethered-Biginelli products **32**.

SCHEME 7



This five-step sequence was employed to prepare six hexahydrotriazaacenaphthalenes (**32a**−**f**, Table 5). The overall yields for these syntheses ranged from 11 to 42%. For the hexahydrotriazaacenaphthalene products (n = 1), the yields for the tethered Biginelli reactions ranged from 51 to 90%. However, little diastereoselectivity was observed, a result that stands in contrast to the tethered Biginelli reactions reported previously from our laboratories.[9b,13,15] The *syn* relative configuration was slightly favored (3:1, verified by ^{1}H NMR NOE correlations) for several of these products (**32a**,**c**, and **e**). Other hexahydrotriazaacenaphthalene adducts were isolated as 1:1 mixtures of epimers. In all cases, the *syn* and *anti* epimers were cleanly separated using standard flash chromatography techniques.

In addition to the preparation of triazaacenaphthalene structures, one derivative that incorporates a fused piperidine ring, hexahydro-1*H*-1,9,9b-diazaphenalene **32g**, was also synthesized. The inclusion of the six-membered piperidine ring resulted in a lower yield for the tethered Biginelli reaction (27%). However, this reaction proceeded with high diastereoselection to produce exclusively the *syn* product.

Discussion

Biginelli strategies utilizing pyrazole carboxamidine **17** or triazone-protected guanidine **20** enable the concise and general synthesis of 2-imino-5-carboxy-3,4-dihydropyrimidines. Only a few members of this class of heterocycles had previously been prepared using Biginelli reactions, which suffered from low yields or lack of generality in one or more of the reactants.[21,22]

(31) The monoprotected dialdehyde precursors were synthesized as described in: Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759−762. Spectral data were consistent with previously published data. For **28a**: Griesbaum, K.; Jung, I. C.; Mertens, H. *J. Org. Chem.* **1990**, *55*, 6024−6027. For **28b**: Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033−1041.

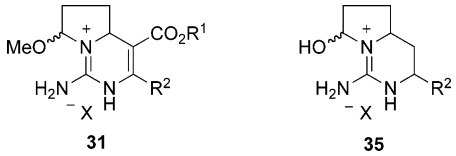


FIGURE 2.

There are advantages and limitations to each method developed during the present study. The Biginelli reaction with pyrazole carboxamidine **17** followed by aminolysis utilizes relatively mild conditions throughout. However, the initial Biginelli step involves a slow dehydration that requires prolonged heating to drive to completion. In addition, efficient aminolysis is dependent upon the introduction of a Boc substituent. This protection step and the subsequent deprotection reaction add two steps to the route. Despite these limitations, this method is preferable for substrates having sensitive functionality, as most of the chemistry is relatively mild. In contrast, the synthesis of 2-imino-5-carboxy-3,4-dihydropyrimidines from triazone guanidine **20** requires only two steps: the Biginelli reaction, which is complete within 12 h, and the final deprotection step. This Biginelli reaction is more general in scope than that employing pyrazole carboxamidine **17**, as every aldehyde surveyed provided the desired adduct. The major limitation of this second strategy is the harsh deprotection step (strong acid, heat), which is incompatible with some functionality. Taken together, these two strategies provide ready access to a wide range of 2-imino-5-carboxy-3,4-dihydropyrimidines. Both strategies provide these products as racemates.[32]

We have applied the pyrazole carboxamidine **17** Biginelli−aminolysis sequence to masked dialdehydes to ultimately generate tetrahydropyrrolopyrimidinium intermediates **31**, which were transformed by tethered Biginelli reactions to a variety of hexahydrotriazaacenaphthalenes **32**. This chemistry provides access to the core structures of the crambescidin and the batzelladine alkaloids in a succinct five-step sequence from readily available starting materials.

The standard Knoevenagel conditions used in this study for the tethered Biginelli condensation (1 equiv of morpholinium acetate, trifluoroethanol) were previously shown to favor *syn* stereoselection with similar substrates.[15a] Thus, tethered Biginelli reactions of hexahydropyrrolopyrimidinium substrates **35** (Figure 2) proceeded with up to 9:1 stereoselectivity under essentially identical conditions.[15] These studies showed that the stereochemical outcome of this reaction can be rather solvent and temperature dependent, with lower temperatures and more polar solvents improving stereoselectivity.[15a] We were, therefore, somewhat surprised by the low selectivities observed for tethered Biginelli reactions of tetrahydropyrrolopyridinium substrates **31**. The incorporation of a second double bond in substrates of type **31** compared to those of type **33** (Figure 2) leads to some flattening of the bicyclic ring system. This change may account for the erosion in stereoselectivity.

The chemistry reported herein can likely be used to synthesize several heterocyclic architectures in addition to hexahydrotriazaacenaphthalenes. One example was demonstrated, the short construction of hexahydro-1*H*-1,9,9b-triazaphenalene **32g**. This example demonstrates the utility of this chemistry for preparing decidedly non-natural analogues of the crambescidin and the batzelladine alkaloids. In addition to alternative sizes for the central fused ring and the substituents R^1-R^4, a variety of other analogues undoubtedly can be synthesized from core structures of type **32**.

Conclusion

Natural products that contain guanidine units within six-membered heterocyclic rings possess diverse biological activities. The short synthesis of 2-imino-5-carboxy-1,4-dihydropyrimidines and hexahydrotriazaacenaphthalenes reported herein will likely find use for the synthesis of focused libraries of guanidine alkaloid-like structures. We are applying and extending the strategies described herein to the preparation of such libraries in order to more completely probe the biology of these fascinating guanidine-containing heterocycles.

Experimental Section[33]

6-Methyl-4-phenyl-2-pyrazol-1-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (18a). Representative Procedure for Synthesis of Biginelli Products 18. Benzaldehyde (1.14 mL, 11.3 mmol), ethyl acetoacetate (1.45 mL, 11.3 mmol), pyrazole carboxamidine hydrochloride **17** (1.86 g, 12.5 mmol), and $NaHCO_3$ (3.8 g, 45 mmol) were heated in DMF (16.5 mL) at 70 °C for 48 h. After cooling to room temperature, the solution was diluted with water (50 mL) and washed with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 20% Et_2O in hexanes → 40% Et_2O in hexanes) to give compound **18a** as a pale yellow oil (2.65 g, 73% yield, a 1.6:1 mixture of tautomers): ^{1}H NMR (500 MHz, DMSO-d_6) major tautomer δ 9.56 (d, J = 3.5 Hz, 1 H), 8.46 (d, J = 3 Hz, 1 H), 7.86 (s, 1 H), 7.37−7.31 (m, 4 H), 7.28−7.23 (m, 1 H), 6.58−6.57 (m, 1 H), 5.59 (d, J = 3.5 Hz, 1 H), 4.08−4.03 (m, 2 H), 2.42 (s, 3 H), 1.14 (t, J = 7 Hz, 3 H) ppm; minor tautomer δ 9.88 (s, 1 H), 8.34 (d, J = 2.5 Hz, 1 H), 7.83 (s, 1 H), 7.37−7.31 (m, 4 H), 7.28−7.23 (m, 1 H), 6.54−6.53 (m, 1 H), 5.65 (s, 1 H), 4.08−4.03 (m, 2 H), 2.47 (s, 3 H), 1.13 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) all peaks from both tautomers δ 165.9, 165.8, 156.6, 146.9, 146.2, 145.5, 144.5, 143.1, 141.5, 141.3, 128.8, 128.4, 128.3, 128.0, 127.6, 127.0, 126.8, 126.5, 109.1, 108.6, 103.8, 99.8, 59.3, 59.3, 58.0, 52.7, 23.0, 17.6, 14.1, 14.0 ppm; IR (thin film) 3381, 3335, 2983, 2931, 1743, 1716, 1702, 1628, 1532, 1485, 1395, 1370, 1263, 1240, 1200, 1171, 1151, 1091, 1307 cm^{-1}; HRMS (ESI) m/z 311.1513 (311.1508 calcd for $C_{17}H_{19}N_4O_2^+$ $[MH]^+$).

4-Methyl-6-phenyl-2-pyrazol-1-yl-6*H*-pyrimidine-1,5-dicarboxylic acid 1-*tert*-butyl ester 5-ethyl ester (19a). Representative Procedure for Synthesis of Boc-Protected Biginelli Adducts 19. Compound **18a** (262 mg, 0.84 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 285 mg, 1.01 mmol) were dissolved in MeCN (3.0 mL) under a N_2 atmosphere. DMAP (10 mg, 78 μmol) was added, and the solution was maintained at room temperature for 12 h. The solvent was removed in vacuo, and the residue was recrystallized from EtOH to give **19a** as a colorless solid (230 mg, 67%, mp 144−145 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 7.71 (s, 1 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.32−7.29 (m, 2 H), 7.27 (m, 1 H), 6.45 (s, 1 H), 6.39 (s, 1 H), 4.31−4.22 (m, 2 H), 2.61 (s, 3 H), 1.35 (s, 9 H), 1.29 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165. 7, 153.5, 151.6, 143.3, 143.1, 138. 5, 129.5, 128.5, 128.1, 126.9, 113.6, 108.6, 83.7, 60.7, 55.0, 27.6, 21.2, 14.3 ppm; IR (thin film) 2983, 2935, 1732, 1707, 1702, 1623, 1564, 1461, 1397, 1370, 1300, 1267, 1231, 1143, 1090, 1038, 963, 908 cm^{-1}; HRMS (ESI) m/z 433.1867 (433.1852 calcd for $C_{22}H_{26}N_4O_4$-

(32) Some progress in orchestrating asymmetric Biginelli reactions has been described. See: Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386−16387.

(33) General experimental details are described in the Supporting Information.

Na^+ $[MNa]^+$). Anal. Calcd for $C_{22}H_{26}N_4O_4$: C, 64.37; H, 6.38; N, 13.65. Found: C, 64.24; H, 6.45; N, 13.65.

2-Amino-4-methyl-6-phenyl-6*H*-pyrimidine-1,5-dicarboxylic acid 1-*tert*-butyl ester 5-ethyl ester (16a). Representative Procedure for Synthesis of Aminolysis Products 16. A solution of compound **19a** (219 mg, 0.53 mmol), ammonium chloride (14 mg, 0.27 mmol), and THF (2 mL) was cooled to 0 °C, and ammonia gas was bubbled through for 30 min. The resulting solution was heated in a sealed tube at 70 °C for 12 h. After cooling to room temperature, the solvent was removed in vacuo, and the residue was purified by recrystallization (EtOH) to give **16a** as a colorless solid (147 mg, 77% yield, mp 169−170 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br s, 1 H), 7.40−7.38 (m, 2 H), 7.35−7.29 (m, 3 H), 6.25 (s, 1 H), 4.17 (q, J = 6.5 Hz, 2 H), 2.37 (s, 3 H), 1.55 (s, 9 H), 1.29 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 156.0, 153.3, 151.8, 142.3, 128.6, 128.0, 127.0, 104.4, 84.7, 59.8, 55.7, 28.1, 22.2, 14.5 ppm; IR (thin film) 3370, 3011, 2986, 1717, 1697, 1651, 1607, 1519, 1370, 1342, 1337, 1297, 1236, 1148, 1115, 1063 cm^{-1}; HRMS (ESI) *m*/*z* 360.1929 (360.1923 calcd for $C_{19}H_{26}N_3O_4^+$ $[MH]^+$). Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.08; H, 7.12; N, 11.85.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-ylidene ammonium trifluoroacetate (10a). Representative Procedure for Synthesis of Heterocyclic Guanidines 10. Method A: Compound **16a** (674 mg, 1.88 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under nitrogen. TFA (2.5 mL) was added, and the resulting solution was stirred for 1 h at room temperature. The solvent and excess TFA were removed under reduced pressure, and the resulting residue was purified by trituration with Et_2O to give trifluoroacetate salt **10a** as a colorless solid (629 mg, 90%): ^{1}H NMR (500 MHz, $CDCl_3$:CD_3OD (1:1)) δ 7.34−7.31 (m, 2 H), 7.28−7.26 (m, 3 H), 5.43 (s, 1 H), 4.10−4.04 (m, 2 H), 2.42 (s, 3 H), 1.14 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD (1:1)) δ 164.9, 151.0, 143.4, 141.6, 128.8, 128.4, 126.4, 103.6, 60.5, 53.3, 17.2, 13.6 ppm; IR (thin film) 3247, 3065, 2984, 2875, 1690, 1637, 1556, 1496, 1457, 1386, 1370, 1329, 1273, 1241, 1090, 910 cm^{-1}; HRMS (ESI) *m*/*z* 260.1400 (260.1399 calcd for $C_{14}H_{19}N_3O_2^+$ $[MH]^+$). Anal. Calcd for $C_{16}H_{18}N_3O_6F_3$: C, 51.48; H, 4.86; N, 11.26. Found: C, 51.59; H, 4.87; N, 11.19. **Method B:** Compound **21a** (189 mg, 0.51 mmol) was dissolved in 6 N HCl (10 mL) and heated to 60 °C in a sealed tube for 24 h. After cooling to room temperature, the reaction solution was then extracted with CH_2Cl_2 (8 × 10 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 10% MeOH in CH_2Cl_2) to give the HCl salt of **10a** as a colorless solid (126 mg, 84%).

5-Benzyl-1,3-dimethyl-[1,3,5]triazinan-2-one (25). Benzylamine (5 mL, 45.8 mmol), formaldehyde (37% w/w solution, 7.5 mL, 91.6 mmol), and *N*,*N*′-dimethylurea (4.03 g, 45.8 mmol) were charged to a reaction flask equipped with a reflux condenser and heated to 100 °C under an argon atmosphere for 16 h. After cooling to room temperature, the reaction was quenched by the addition of H_2O (25 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and washed with brine (1 × 25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, Et_2O → 10% MeOH in Et_2O) to give **25** as a colorless solid (7.46 g, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.16 (m, 5 H), 4.00 (s, 4 H), 3.80 (s, 2 H), 2.74 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 137.5, 129.0, 128.5, 127.6, 67.7, 55.3, 32.4 ppm; IR (thin film) 3452, 2924, 2869, 1629, 1514, 1453, 1417, 1404, 1297, 1151, 1024 cm^{-1}; HRMS (ESI) *m*/*z* 242.1276 (242.1269 calcd for $C_{12}H_{17}N_3ONa^+$ $[MNa]^+$).

1,3-Dimethyl-[1,3,5]triazinan-2-one (26). 5-Benzyl-1,3-dimethyl-[1,3,5]triazinan-2-one **25** (1.0 g, 4.56 mmol) was dissolved in EtOH (25 mL). To this solution was added Pd/C (10%) (140 mg), and the resulting mixture was heated to 65 °C under an H_2 atmosphere (750 psi) for 18 h. After cooling to room temperature, the suspension was then filtered through Celite, and the eluent was concentrated by rotary evaporation to give **26** as a colorless solid (567 mg, 96% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (s, 4 H), 2.68 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 63.1, 31.5 ppm; IR (thin film) 3420, 3283, 2939, 2871, 1624, 1523, 1418, 1405, 1301, 1029, 906 cm^{-1}; HRMS (ESI) *m*/*z* 152.0801 (152.0800 calcd for $C_5H_{11}N_3ONa^+$ $[MNa]^+$).

***tert*-Butyloxycarbonylimino-[(3,5-dimethyl-4-oxo-[1,3,5]triazinan-1-yl)methyl]carbamic acid *tert*-butyl ester (28).** *N*,*N*′-Bis(*t*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine **27** (7.46 g, 24.1 mmol) and 1,3-dimethyl-[1,3,5]triazinan-2-one **26** (3.73 g, 28.9 mmol) were dissolved in dry THF (10 mL) under argon in a flame-dried flask. This solution was heated at 70 °C for 24 h. After cooling to room temperature, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, 4% MeOH in CH_2Cl_2) to give **28** as a colorless solid (4.63 g, 53% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (br s, 1 H), 4.67 (s, 4 H), 2.89 (s, 6 H), 1.46 (s, 18 H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 157.1, 153.7, 81.6, 62.1, 33.0, 28.1 ppm; IR (thin film) 3179, 2981, 2934, 1750, 1636, 1607, 1517, 1392, 1288, 1254, 1226, 1131, 1124 cm^{-1}; HRMS (ESI) *m*/*z* 394.2064 (394.2066 calcd for $C_{16}H_{29}N_5O_5Na^+$ $[MNa]^+$).

3,5-Dimethyl-4-oxo-[1,3,5]triazinane-1-carboxamidine trifluoroacetate salt (20). Compound **28** (4.93 g, 13.3 mmol) was dissolved in CH_2Cl_2 (18.6 mL) under argon, and TFA (18.6 mL) was added. The resulting solution was maintained at room temperature for 1 h, the solvent was removed under reduced pressure, and the resulting residue was crystallized from Et_2O to give **20** as a colorless solid (3.8 g, 100% yield, mp 179−181 °C): ^{1}H NMR (500 MHz, CD_3OD) δ 4.73 (s, 4 H), 2.88 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 161.3, 158.4, 63.3, 33.1 ppm; IR (thin film) 3336, 2931, 2882, 2476, 1602, 1527, 1423, 1406, 1313, 1120, 1035, 975 cm^{-1}; HRMS (ESI) *m*/*z* 172.1204 (172.1198 calcd for $C_6H_{14}N_5O^+$ $[MH]^+$). Anal. Calcd for $C_8H_{14}F_3N_5O_3$: C, 33.69; H, 5.00; N, 24.55. Found: C, 33.83; H, 5.00; N, 24.43.

2-(3,5-Dimethyl-4-oxo-[1,3,5]triazinan-1-yl)-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (21a). Representative Procedure for Synthesis of Biginelli Products 21. Compound **20** (293 mg, 1.71 mmol), ethyl acetoacetate (0.2 mL, 1.56 mmol), benzaldehyde (0.16 mL, 1.56 mmol), and $NaHCO_3$ (575 mg, 6.85 mmol) were added to DMF (2.5 mL) under a nitrogen atmosphere. This mixture was heated at 70 °C for 22 h. The reaction was cooled to room temperature and poured over crushed ice (25 g). The resulting suspension was extracted with Et_2O (1 × 75 mL) and CH_2Cl_2 (3 × 25 mL), and the organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting residue was recrystallized from Et_2O to give **21a** as a colorless solid (425 mg, 73% yield, mp 198−200 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.21 (m, 5 H), 5.39 (s, 1 H), 4.79−4.72 (m, 4 H), 4.06−4.02 (m, 2 H), 2.77 (s, 6 H), 2.39 (s, 3 H), 1.19 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 158.7, 156.2, 153.0, 145.2, 128.5, 127.6, 126.5, 102.2, 61.8, 60.0, 54.2, 32.7, 24.0, 14.4 ppm; IR (thin film) 3252, 2981, 2932, 2904, 2886, 2880, 1664, 1629, 1599, 1522, 1503, 1372, 1339, 1303, 1217, 1126, 1061, 1033, 968, 910 cm^{-1}; HRMS (ESI) *m*/*z* 372.2030 (372.2036 calcd for $C_{19}H_{26}N_5O_3^+$ $[MNa]^+$). Anal. Calcd for $C_{19}H_{25}N_5O_3$: C, 61.44; H, 6.78; N, 18.85. Found: C, 61.22; H, 6.94; N, 18.67.

4-(3,3-Dimethoxypropyl)-6-methyl-2-pyrazol-1-yl-1,4-dihydropyrimidine-5-carboxylic acid ethyl ester (33a). Representative Procedure for Synthesis of Biginelli Products 33. Compound **17** (1.24 g, 8.32 mmol), ethyl acetoacetate (0.96 mL, 7.57 mmol), and aldehyde **29a** (1.0 g, 7.57 mmol) were dissolved in DMF buffered with $NaHCO_3$ (2.54 g, 30.3 mmol) and heated under a N_2 atmosphere for 48 h. The mixture was cooled to room temperature, diluted with water (20 mL), and the resulting solution was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (silica gel, 100% Et_2O) to give **33a** as a yellow oil (1.58 g, 62% yield, a 1.3:1 mixture of tautomers): ^{1}H NMR (500 MHz, $CDCl_3$) major tautomer δ 8.11 (d, J = 5 Hz, 1 H), 7.87 (s, 1 H), 7.43 (d, J = 1 Hz, 1 H), 6.25−

6.24 (m, 1 H), 4.55 (t, J = 5 Hz, 1 H), 4.23 (t, J = 5 Hz, 1 H), 4.09−4.00 (m, 2 H), 3.12 (s, 6 H), 2.21 (s, 3 H), 1.71−1.65 (m, 1 H), 1.59−1.49 (m, 3 H), 1.13 (q, J = 7 Hz, 3 H) ppm; minor tautomer δ 8.20 (d, J = 5 Hz, 1 H), 7.48 (d, J = 1 Hz, 1 H), 7.35 (d, J = 2.5 Hz, 1 H), 6.25−6.24 (m, 1 H), 4.48−4.47 (m, 1 H), 4.18 (t, J = 5 Hz, 1 H), 4.09−4.00 (m, 2 H), 3.14 (s, 3 H), 3.12 (s, 3 H), 2.20 (s, 3 H), 1.71−1.65 (m, 1 H), 1.59−1.49 (m, 3 H), 1.14 (q, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) all peaks from both tautomers δ 166.5, 157.2, 147.4, 144.8, 142.6, 141.1, 141.0, 128.4, 127.1, 108.7, 108.5, 104.9, 104.5, 104.4, 101.3, 59.68, 59.7, 54.4, 53.0, 52. 6, 52.5, 52.4, 50.2, 32.0, 31.8, 27.6, 27.2, 23.2, 18.6, 14.3, 14.3 ppm; IR (thin film) 3389, 3320, 2982, 2955, 2937, 1697, 1627, 1531, 1484, 1394, 1377, 1241, 1200, 1126, 1105, 1071, 1038 cm^{-1}; HRMS (ESI) m/z 359.1689 (359.1695 calcd for $C_{16}H_{24}N_4O_4Na^+$ $[MNa]^+$).

6-(3,3-Dimethoxypropyl)-4-methyl-2-pyrazol-1-yl-6*H*-pyrimidine-1,5-dicarboxylic acid 1-*tert*-butyl ester 5-ethyl ester (34a). Representative Procedure for Synthesis of Boc-Protected Biginelli Products 34. Compound **33a** (1.45 g, 4.31 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 1.13 g, 5.17 mmol) were dissolved in MeCN (17.0 mL) under a N_2 atmosphere. DMAP (53 mg, 0.43 mmol) was added, and the solution was stirred at room temperature for 12 h. The solvent was removed in vacuo, and the residue was recrystallized from Et_2O/hexanes to give **34a** as a colorless solid (1.36 g, 73%, mp 114−115 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 2.5 Hz, 1 H), 7.72 (s, 1 H), 6.44 (s, 1 H), 5.19 (dd, J = 10, 4 Hz, 1 H), 4.39 (t, J = 6 Hz, 1 H), 4.32−4.20 (m, 2 H), 3.30 (s, 3 H), 3.27 (s, 3 H), 2.43 (s, 3 H), 1.94−1.87 (m, 1 H), 1.80−1.73 (m, 1 H), 1.65−1.58 (m, 1 H), 1.54−1.46 (m, 1 H), 1.34 (t, J = 7 Hz, 3 H), 1.25 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 152.5, 151.4, 143.0, 129.5, 114.9, 108.6, 104.18, 83.3, 60.6, 53.2, 52.9, 52.6, 27.8, 27.7, 27.6, 26.8, 21.2, 14.4 ppm; IR (thin film) 3394, 2982, 2935, 2831, 1774, 1732, 1709, 1650, 1623, 1567, 1460, 1398, 1370, 1301, 1288, 1230, 1142, 1070 cm^{-1}; HRMS (ESI) m/z 459.2212 (459.2220 calcd for $C_{21}H_{32}N_4O_6Na^+$ $[MNa]^+$).

2-Amino-6-(3,3-dimethoxypropyl)-4-methyl-6*H*-pyrimidine-1,5-dicarboxylic acid 1-*tert*-butyl ester 5-ethyl ester (30a). Representative Procedure for Synthesis of Products 30. Compound **34a** (1.15 g, 2.63 mmol) and ammonium chloride (71 mg, 1.32 mmol) were dissolved in THF (17 mL), cooled to 0 °C, and ammonia gas was bubbled through for 30 min. The resulting solution was sealed in a glass tube and stirred at 70 °C for 12 h. After cooling to room temperature, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, 40% Et_2O in hexanes → 100% Et_2O → 10% MeOH in Et_2O) to give product **30a** as a colorless solid (0.90 g, 88% yield, mp 110−111 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (br s, 2 H), 5.21 (s, 1 H), 4.30 (s, 1 H), 4.16 (q, J = 7 Hz, 2 H), 3.26 (s, 6 H), 2.21 (s, 3 H), 1.55−1.54 (m, 4 H), 1.52 (s, 9 H), 1.26 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 156.1, 153.0, 151.6, 104.1, 84.0, 59.5, 52. 7, 52.65, 51.9, 28.9, 28.0, 27.9, 21.5, 14.4 ppm; IR (thin film) 3410, 2982, 2936, 1716, 1645, 1597, 1514, 1371, 1343, 1289, 1265, 1241, 1141, 1064 cm^{-1}; HRMS (ESI) m/z 408.2104 (408.2111 calcd for $C_{18}H_{31}N_3O_6Na^+$ $[MNa]^+$). Anal. Calcd for $C_{18}H_{31}N_3O_6$: C, 56.09; H, 8.11; N, 10.90. Found: C, 56.39; H, 8.05; N, 10.85.

3-Ethoxycarbonyl-8-methoxycarbonyl-4,7-dimethyl-1,2,2a,5,6,-8a-hexahydro-5,6,8b-triazaacenaphthalene (32a). Representative Procedure for Synthesis of Triazaacenaphthalenes 32. Compound **30a** (200 mg, 0.52 mmol) was stirred in 50% TFA:CH_2Cl_2 (1.4 mL) under a N_2 atmosphere for 1 h. The solvent and excess TFA were removed under reduced pressure, and the residue was placed under high vacuum for 8 h. The residue was then dissolved in trifluoroethanol (1 mL), and to this solution were added morpholinium acetate (84 mg, 0.57 mmol), Na_2SO_4 (81 mg, 0.57 mmol), and methyl acetoacetate (0.16 mL, 1.56 mmol). This mixture was heated at 70 °C for 72 h and then filtered to remove Na_2SO_4, concentrated, and the residue was purified by chromatography (silica gel, 1% MeOH in CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give compound **32a** as a mixture of diastereomers. These epimers were separated by chromatography (silica gel, EtOAc) to give *syn*-**32a** (119 mg, 52% yield) and *anti*-**32a** (40 mg, 18% yield) as tan trifluoroacetate salt solids. The relative configuration of the angular hydrogens flanking the pyrrolidine nitrogen was verified by NOESY cross-peaks. *syn*-**32a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (q, J = 5 Hz, 2 H), 4.27−4.20 (m, 1 H), 4.18−4.12 (m, 1 H), 2.65−2.62 (m, 2 H), 2.29 (s, 6 H), 1.94−1.90 (m, 2 H), 1.30 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.9, 153.1, 152.3, 149.6, 103.7, 103.4, 60.1, 55.8, 51.1, 33.1, 33.0, 20.3, 20.1, 14.6 ppm; IR (thin film) 3283, 3145, 2983, 2948, 2872, 2840, 1691, 1685, 1617, 1522, 1443, 1372, 1338, 1317, 1290, 1269, 1248, 1203, 1183, 1130, 1104, 1079 cm^{-1}; HRMS (ESI) m/z 320.1604 (320.1610 calcd for $C_{16}H_{22}N_3O_4^+$ $[M]^+$). *anti*-**32a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27−4.15 (m, 4 H), 3.75 (s, 3 H), 2.40−2.38 (m, 2 H), 2.37 (s, 6 H), 1.63−1.60 (m, 2 H), 1.30 (t, J = 7 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.8, 153.1, 152.2, 149.6, 103.7, 103.4, 60.1, 55.8, 51.1, 33.1, 33.0, 20.3, 20.1, 14.6 ppm; IR (thin film) 3190, 3078, 2983, 2908, 2779, 1702, 1697, 1619, 1569, 1541, 1433, 1378, 1320, 1280, 1268, 1238, 1201, 1187, 1166, 1089 cm^{-1}; HRMS (ESI) m/z 320.1616 (320.1610 calcd for $C_{16}H_{22}N_3O_4^+$ $[M]^+$).

Acknowledgment. This research was supported by NIH (HL-25854), and Pharma Mar. Postdoctoral fellowship support for B.L.N. from the Canadian Institutes of Health Research Institute of Infection and Immunity is gratefully acknowledged. NMR and mass spectra were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061199M