ORGANIC LETTERS

2003
Vol. 5, No. 23
4485−4488

Assembling Polycyclic Bisguanidine Motifs Resembling Batzelladine Alkaloids by Double Tethered Biginelli Condensations

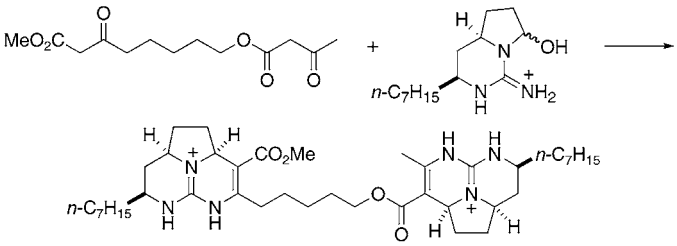
Frederick Cohen,[†] Shawn K. Collins,[‡] and Larry E. Overman*

Department of Chemistry, 516 Rowland Hall, University of California−Irvine, Irvine, California, 92697−2025

leoverma@uci.edu

Received September 17, 2003

ABSTRACT



Double tethered Biginelli condensations furnish linked polycyclic bisguanidines or bisureas. Alteration of the bis-β-ketoester component allows bispolycyclic guanidine motifs to be constructed that resemble natural batzelladine alkaloids or have novel linkages.

Members of the batzelladine family of sponge-derived alkaloids are rare examples of small natural products that regulate protein−protein interactions.[1,2] Batzelledines A and B (**1**) were the first low-molecular weight natural products reported to inhibit the binding of HIV gp-120 to human CD4, a critical step in the life cycle of the AIDS virus,[1] whereas batzelladines F (**2**)−I induce dissociation of the protein tyrosine kinase p56 from its complex with CD4.[2a] Various batzelladine alkaloids and analogues also inhibit HIV envelope-mediated cell fusion.[3] The most complex batzelladine alkaloids, exemplified by batzelladines B (**1**) and F (**2**), contain two polycyclic guanidine units, whereas batzelladines C, D (**3**), and E display a single tricyclic guanidine moiety (Figure 1). The decahydro- or octahydro-5,6,8b-triazaacenaphthalene unit that is the common structural feature of the batzelladine alkaloids occurs with both the cis and trans stereorelationships of the angular hydrogens that flank the pyrrolidine nitrogen.

The batzelladine family of polycyclic guanidine alkaloids has stimulated many synthetic endeavors.[4−7] Some of these studies established the relative configuration[5c,f−h,6c] and constitution[6c] of various batzelladine alkaloids, whereas others defined their absolute configuration.[5i,6j] Total syntheses of (−)-batzelladine D (**3**),[6b] (±)-batzelladine D (**3**),[5k] (±)-batzelladine E,[5f] and (−)-batzelladine F (**2**)[6c] have been accomplished.

Although significant advances in synthesis and structural verification of the batzelladine alkaloids have been achieved, identification of the essential features required to impart biological activity to these marine natural products remains a long-standing goal. Investigations of structure−activity

[†] Current address: Department of Medicinal Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080.

[‡] Current address: Université de Montréal, Départemente de Chimie, C.P. 6128, Succursale Centre-ville, Montréal, QC., Canada, H3C 3J7. E-mail: s.collins@umontreal.ca.

(1) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, 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.

(2) (a) 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. (b) Braekman, J. C.; Daloze, D.; Tavares, R.; Hajdu, E.; Vas Soest, R. W. M. *J. Nat. Prod.* **2000**, *63*, 193−196.

(3) Bewley, C. A.; Cohen, F.; Collins, S. K.; Overman, L. E. Manuscript in preparation.

(4) For reviews of early studies, see: Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, 339−365.

10.1021/ol0357999 CCC: $25.00
Published on Web 10/15/2003

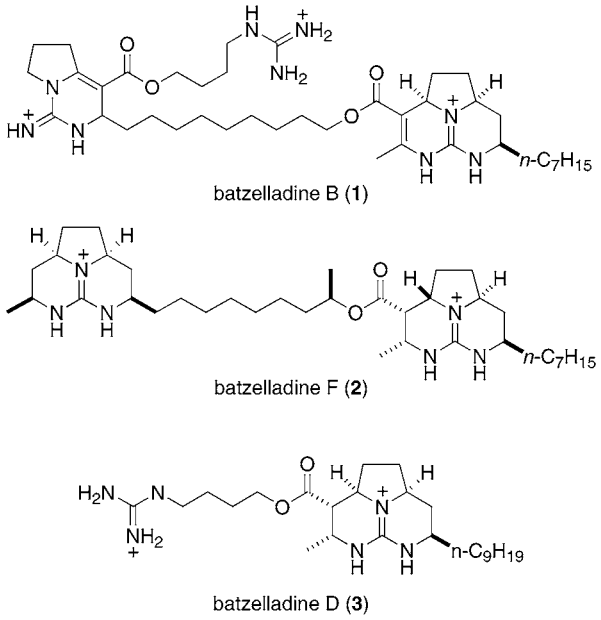
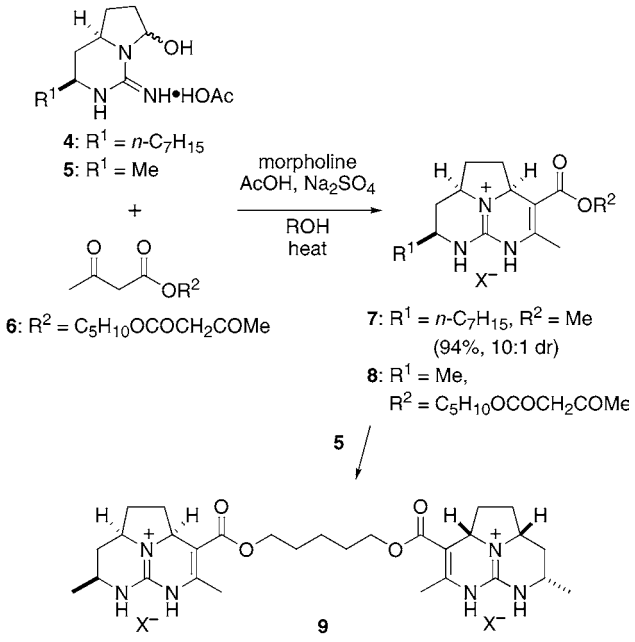


Figure 1. Representative batzelladine alkaloids.

relationships would be greatly facilitated by a streamlined synthesis of batzelladine-like bisguanidines. Herein we report our initial investigations into the use of double tethered Biginelli cyclizations[7,8] to synthesize molecular architectures that resemble naturally occurring batzelladine alkaloids.

The tethered Biginelli reaction has played a central role in our laboratory's total syntheses of crambescidin and batzelladine alkaloids.[6,7] For example, morpholinium acetate-promoted condensation of guanidine aldehyde **4** with methyl acetoacetate in trifluoroethanol (TFE) at 90 °C provided the right-hand fragment **7** of batzelladine B (**1**) in 94% yield with 10:1 stereoselectivity for forming the isomer having a cis relationship of the angular hydrogens (Scheme 1).[6a] If the nucleophilic component in such a reaction were a bis-β-ketoester, Biginelli condensation with a tethered guanidine aldehyde should rapidly assemble hexacyclic bisguanidine analogues of complex batzelladines such as **9**. Our initial investigation of this proposal is the subject of this communication.

Scheme 1. Single and Double Tethered Biginelli Reactions



To study double tethered Biginelli cyclizations for accessing molecular architectures resembling naturally occurring batzelladines, the series of bis-β-ketoesters summarized in Figure 2 was prepared. These syntheses were accomplished using standard methods that exploited transformations developed by Taber[9] and Wieler;[10] experimental details can be found in Supporting Information.

Exploratory investigations of double tethered Biginelli condensations were carried out at 60 °C using the procedure employed to form **7**.[6a] Under these conditions, the reaction of guanidine aldehyde **5** with bis-β-ketoester **6** produced the double Biginelli product **9** in low yield, the major product being the mono Biginelli adduct **8** (Scheme 1). However, the yield of **9** was improved to 41% when 3.5−4 equiv of **5** were employed. Methanol, which appears to better dissolve the Biginelli monoadduct, could also be used as the solvent.

Results of double tethered Biginelli condensations of two representative tethered guanidine aldehydes and the series of bis-β-ketoesters shown in Figure 2 are summarized in Table 1. The reaction reported in entry 2 is typical, providing two stereoisomeric bisguanidine products that could be separated by HPLC. The major product **16**, showing only

(5) For studies from other laboratories, see: (a) Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Abdul Malik, K. M. *J. Chem Soc., Chem. Commun.* **1994**, 119−121. (b) Rao, A. V. R.; Gurjar, M. K.; Vasudevan, Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980. (c) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977−6980. (d) Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Abdul Malik, K. M. A. *Tetrahedron Lett.* **1996**, *37*, 6043−6946. (e) Louwrier, S.; Ostendorf, M.; Tuynman, A.; Hiemstra, H. *Tetrahedron Lett.* **1996**, *37*, 905−908. (f) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697−5700. (g) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481−9488. (h) Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C. *Tetrahedron* **1999**, *55*, 6547−6554. (i) Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551−1554. (j) Nagasawa, K.; Koshino, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 4155−4158. (k) Ishiwata, T.; Hino, T.; Koshino, H.; Hasimoto, Y.; Nakata, T.; Nagasawa, K. *Org. Lett.* **2002**, *4*, 2921−2924.

(6) For our studies in this area, see: (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.

(7) For the use of tethered Biginelli condensations for stereocontrolled assembly of decahydro- and octahydro-5,6,8b-triazaacenaphthalenes, see: ref 6 and: (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) McDonald, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520−1528. (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.

(8) For a recent review of the classical Biginelli reaction, see: Kappe, O. C. *Acc. Chem. Res.* **2000**, *33*, 879−888.

(9) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618−3619.

(10) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702−6704.

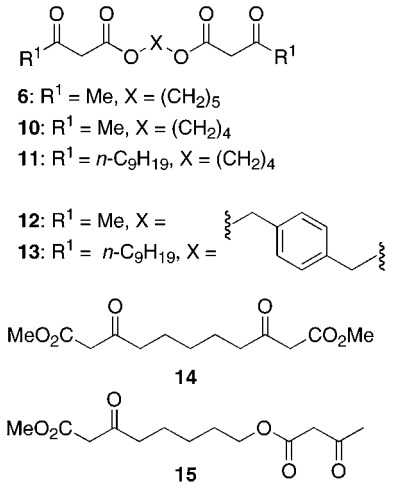
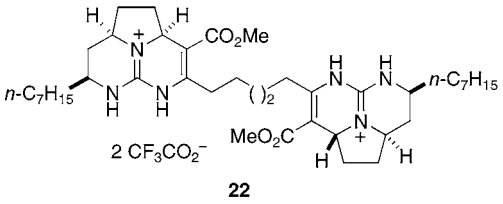
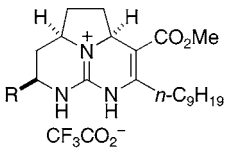


Figure 2. Bis-β-ketoester substrates.

21 signals in its ^{13}C NMR spectrum, was C_2-symmetric. That this product was the expected stereoisomer having a cis relationship of the angular hydrogens[6a] was established by the NOE enhancement (3%) observed between these hydrogens (δ 4.53 dd, J = 9.7, 6.1 Hz; δ 3.78−3.83, m). The minor stereoisomer showed more than 30 resolved signals in the ^{13}C NMR spectra, supporting its assignment as C_1-symmetric isomer **22**.



A variety of bisguanidine motifs can be assembled in this manner. Varying the nature of the symmetrical bis-β-ketoester component allowed the tricyclic guanidine subunits to be linked at their carboxyl carbons (entries 1, 4−7) or be connected by a methylene chain (entry 2). In the former case, the diol linkage could be a simple methylene chain or a chain containing an aromatic spacer. Surprisingly, when bis-β-ketoesters **11** and **13** were employed, double Biginelli condensations with **4** or **5** carried out in methanol provided only the tricyclic guanidine methyl ester **23**. Apparently, the



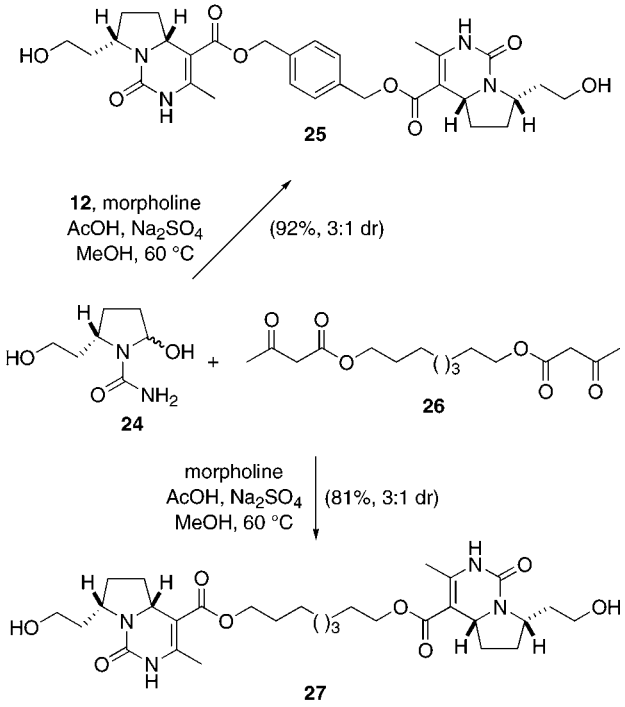
23 (R = Me or n-C_7H_{15})

juxtaposition of the nonyl and ester side chains makes the double Biginelli product susceptible to transesterification.[11] Fortunately, the increased solubility provided by the C9 alkyl chain allowed trifluoroethanol to be employed as the solvent, in which case double Biginelli condensations with these bis-β-keto esters proceeded in useful yields (entries 6 and 7). Gratifyingly, employing unsymmetrical bis-β-ketoester **15** made it also possible to obtain bisguanidine products having linkage patterns similar to those found in batzelladines F−I (entry 3). In all cases reported in Table 1, the corresponding mono Biginelli product (analogous to **7**) was observed as a major byproduct in 5−20% yield.

Not surprisingly, the C_2- and C_1-symmetric products of the double tethered Biginelli reactions reported in Table 1 showed nearly identical physical properties. Nonetheless, these stereoisomers could be resolved by HPLC, although baseline separation was rarely achieved. In all cases, the major C_2-symmetric isomer eluted with a shorter retention time, allowing it to be isolated easily in pure form by preparative HPLC. The later-eluting C_1-symmetric product was typically contaminated with small amounts of the corresponding C_2-symmetric stereoisomer.

Tethered urea aldehydes were found to be superior substrates for double tethered Biginelli reactions (Scheme 2). For example, condensation of 4 equiv of **24**[7a,c] with bis-

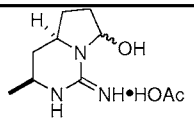
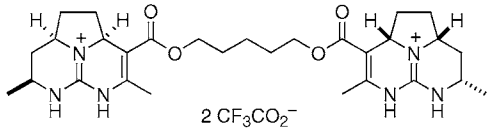
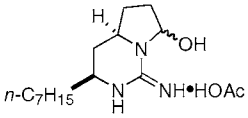
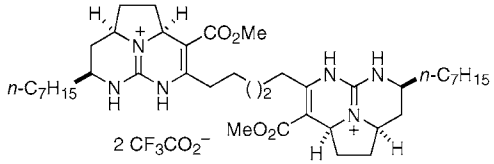
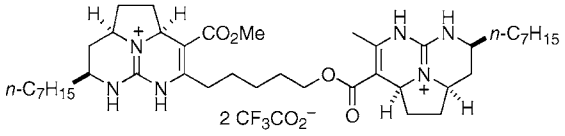
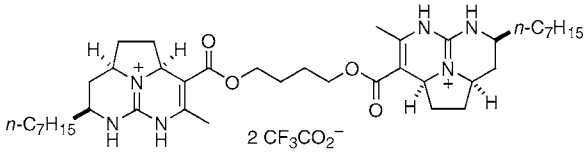
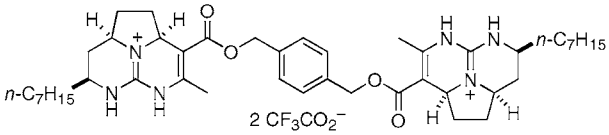
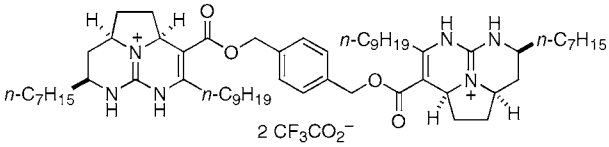
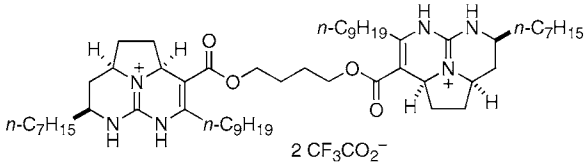
Scheme 2. Double Tethered Biginelli Reaction to Form Bisureas



β-ketoester **12** proceeded in 92% yield to deliver bis-1-oxohexahydropyrrolo[1,2-*c*]pyrimidine carboxylic ester **25** and its C_1-symmetric epimer in 92% yield. Likewise, **27** and its epimer were produced in 81% yield from condensation of **24** and bis-β-ketoester **26**.

In summary, the scope of the tethered Biginelli condensation has been expanded to include the formation of linked bisguanidines and bisureas. Judicious choice of the bis-β-ketoester component allows the octahydro-5,6,6a-triazaacenaphthalene moieties of the bisguanidines to be

Table 1. Bisguanidine Products of Double Tethered Biginelli Condensations[a]

entry	guanidine aldehyde	β-keto-ester	double Biginelli product	Cpd	total yield (%)[b]; yield of C_2 isomer (%)
1	 **5**	**6**		**9**	41[c,d]
2	 **4**	**14**		**16**	58; 35
3	**4**	**15**		**17**	76;[e] 39
4	**4**	**10**		**18**	64; 42
5	**4**	**12**		**19**	38; 25
6	**4**	**13**		**20**	59;34[d]
7	**4**	**11**		**21**	44; 33[d]

[a] Reaction conditions: Bis-β-ketoester (1 equiv), guanidine-aldehyde (4 equiv), morpholine (10 equiv), AcOH (10 equiv), and Na_2SO_4 (10 equiv) in MeOH (0.1 M) at 60 °C for 48−96 h. [b] Combined yields of the C_2- and C_1-symmetric stereoisomers. [c] Minor stereoisomer was not isolated. [d] Trifluoroethanol was the solvent. [e] The major double Biginelli product in this case is not C_2-symmetric; the minor products (37%) were a mixture of two isomers, assumed to each possess one cis and one trans tricyclic guanidine unit.

connected at either their carboxylate carbons, vinylic C4 carbons, or a combination thereof.[12] As myriad variations in the electrophilic and bis-β-ketoester components are possible, the formation of novel linked heterocyclic structures in a large library format should be readily achieved. Results of biological evaluation of the bisguanidines and bisureas prepared during this initial survey will be reported elsewhere.

Acknowledgment. We thank NIH (HL-25854) for financial support. F.C. was supported by an ACS Organic Division Graduate Fellowship sponsored by Pharmacia & Upjohn and S.K.C. by a National Sciences and Engineering Research Council of Canada (NSERC) Postdoctoral Fellowship. NMR and mass spectra were determined at UCI using instruments acquired with the assistance of NSF and NIH shared instrumentation grants.

Supporting Information Available: Experimental procedures and characterization data for bis-β-ketoesters **6**, **10**−**15** and double Biginelli products **9**, **16**−**21**, **25**, and **27**; copies of ^1H and ^{13}C spectra for these new compounds, selected minor double Biginelli products, and **23** (R = n-C_7H_{15}). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0357999

(11) Control experiments showed that bis-β-ketoesters **11** and **13** are stable to the Biginelli reaction conditions in methanol over a period of 7 days, strongly suggesting that methanolysis is occurring after Biginelli condensation.

(12) Such variation should be possible also in the formation of bisureas, although this feature was not demonstrated in the present study.