Application of the Tethered Biginelli Reaction for Enantioselective Synthesis of Batzelladine Alkaloids. Absolute Configuration of the Tricyclic Guanidine Portion of Batzelladine B

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Tethered Biginelli condensation of enantioenriched hexahydropyrrolopyrimidines **8** with β-ketoesters provides efficient asymmetric access to tricyclic guanidines **9** having a syn relationship of the angular C2a and C8a hydrogens. This reaction was employed to realize the first practical enantioselective access to this fragment of batzelladine alkaloids B (**2**) and E (**5**). The efficiency of this strategy is illustrated in the synthesis of the dextrorotatory enantiomer of batzelladine B methanolysis product **10** in 10 steps and 25% overall yield from 2-nonanone and methyl acetoacetate. The asymmetric synthesis of **10** establishes that the absolute configuration of the tricyclic portion of batzelladine B (**2**) is 25a*R*,28*S*,30*R*. The 4-methyl-7-alkyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthalene-3-carboxylic acid subunit, e.g., **29**, of batzelladine alkaloids A (**1**), D (**4**), F (**6**), and G was also prepared for the first time by catalytic hydrogenation of tricyclic guanidines **26** having the 2a,8a-anti stereochemistry.

Introduction

Batzelladines A−I, along with other known guanidine alkaloids such as ptilocaulin, ptilomycalin A (**7**), and crambescins A (**3**), 800 and 816, were isolated by Patil, Faulkner, and co-workers from the Caribbean sponge *Batzella* sp. (Figure 1).[2−4] The batzelladine alkaloids are members of a growing class of guanidine alkaloids that exhibit a broad spectrum of biological activity.[5−7] Batzelladines A (**1**) and B (**2**) were the first low molecular weight natural products reported to inhibit the binding of HIV gp-120 to CD4 cells and, therefore, are potential leads for AIDS therapy.[2] Batzelladines F (**6**) and G induce dissociation of the complex of protein tyrosine kinase $p56^{lck}$ with CD4.[3] Since this association has been reported to be required for antigenic activation, agents of this latter type might be useful for the treatment of autoimmune diseases and allograph rejection.[3]

The relative stereochemistry of the batzelladines has been assigned on the basis of NMR studies and, for **1** and **2**, by comparison of ^{13}C NMR data with those of crambescin A (**3**).[2−4] The absolute configuration of the batzelladine alkaloids is unknown. Several aspects of relative stereochemistry also are as yet unresolved, including the configuration of **1** and **2** at C13, the stereorelationship of the tricyclic fragments of batzelladines F−I, and the stereochemistry of batzelladine F (**6**) at C4, C9, and C16.[8] In an important early synthetic investigation in this area, Snider and co-workers corrected the stereochemistry of the tricyclic portions of batzelladines A (**1**) and D (**4**) to be as depicted in Figure 1.[9] The tricyclic guanidine (decahydro-5,6,8b-triazaacenaphthalene) ring system of the batzelladine alkaloids is also found in pentacyclic guanidine alkaloids of the crambescidin/ptilomycalin A (**7**) families.[6] In both guanidine alkaloid groups, the tricyclic guanidine unit is found with both the syn and anti relationship of the angular hydrogens that flank the pyrrolidine nitrogen.

In 1996, Snider and Chen using a presumed biomimetic strategy described constructions of tricyclic degradation products of several batzelladine alkaloids.[9] More recently, this group reported a total synthesis of (±)-batzelladine E (**5**), which constituted the first total synthesis of a batzelladine alkaloid.[10] Biomimetic constructions of decahydro-5,6,8b-triazaacenaphthalene ring systems through condensation of a dienedione with an amidine or guanidine unit, although beautifully concise, deliver the tricyclic guanidine products in racemic form.[9−11] In the first published synthetic work in this area, Rao and co-workers described the enantioselective preparation of an alcohol analogue of the syn tricyclic guanidine core of batzelladine alkaloids, albeit through a lengthy sequence from an enantiopure azetidine precursor.[12]

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(2) 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.

(3) 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.

(4) Patil, A. D.; Freyer, A. J.; Offen, P.; Bean, M. F.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 704.

(5) Gomes, R.; Berlinck, S. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 119.

(6) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, 377.

(7) Greenhill, J. V.; Pharm, B.; Lue, P. *Prog. Med. Chem.* **1993**, *30*, 203.

(8) The 2a,8a-anti stereochemistry for the left ring of batzelladine F shown in Figure 1 is that proposed by Patil and co-workers.[3] Recent model studies of Murphy[11] and Snider (Snider, B. B. Personal communication to L.E.O., July 21, 1998) suggest that the stereochemistry of batzelladine F at C4 and C9 is epimeric to that shown in Figure 1.

(9) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977.

(10) Snider, B. B.; Chen, J. *Tetrahedron Lett.* **1998**, *39*, 5697.

(11) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *58*, 9481 and references to earlier papers from the Murphy group cited therein.

(12) Rao, A. V. R.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369.

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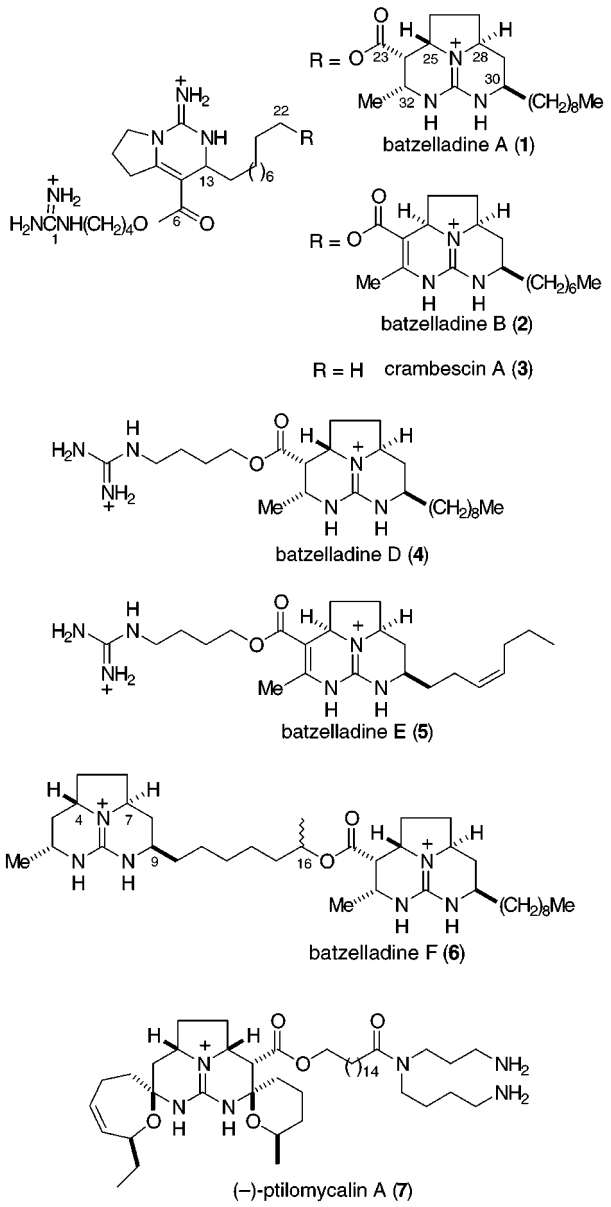
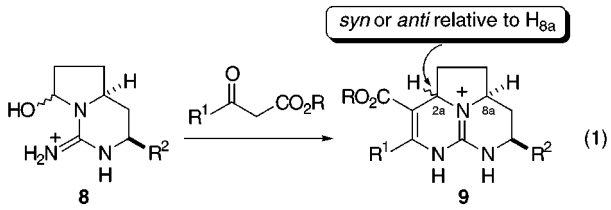
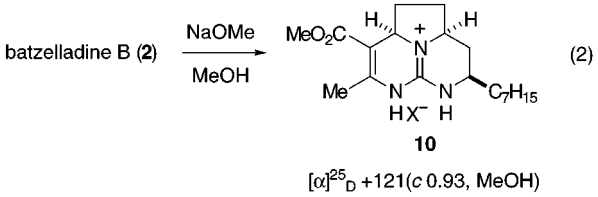


Figure 1. Representative alkaloids isolated from *Batzella* sp.

Since ligands that modulate the association or dissociation of proteins have a myriad of potential applications in biological research and medical therapy,[13] several years ago we initiated efforts to develop a comprehensive strategy for enantioselective synthesis of the various complex guanidine units found in the batzelladine alkaloids.[14] A tethered Biginelli condensation,[15] which was the key strategic reaction of our earlier enantioselective construction of (−)-ptilomycalin A (**7**),[16] was envisaged as the central element of this endeavor. In its most direct formulation, the guanidine and aldehyde components of a Biginelli condensation would be linked as represented in **8** (eq 1). In this paper, we report (a) our investigations of stereoselectivity in the tethered Biginelli condensation



to construct, in enantioselective fashion, the tricyclic guanidine cores **9** of the batzelladine alkaloids, (b) catalytic reduction of the 2a,8a-anti stereoisomer of **9** to achieve the first synthesis of the decahydro tricyclic ester portion of batzelladine alkaloids **1**, **4**, **6**, and batzelladine G, and (c) application of the tethered Biginelli reaction to achieve an efficient synthesis of the dextrorotatory enantiomer of the methanolysis product **10** of batzelladine B (eq 2).[2] This latter enantioselective synthesis establishes that the absolute configuration of the tricyclic portion of batzelladine B (**2**) is as depicted in Figure 1.[14]

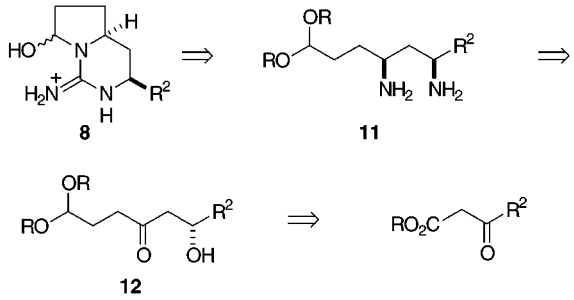


$[\alpha]^{25}_{D}$ +121(*c* 0.93, MeOH)

Results and Discussion

Synthesis of the Hexahydropyrrolopyrimidine Precursor. We envisaged hexahydropyrrolopyrimidine component **8** of the tethered Biginelli condensation coming from *syn*-1,3-diamine **11**, which in turn would derive from enantioenriched *β*-hydroxyketone precursor **12** (Scheme 1). Catalytic asymmetric reduction of *β*-ketoester precursors would be employed to introduce the initial stereocenter, thus allowing convenient access to either enantiomeric series.[17]

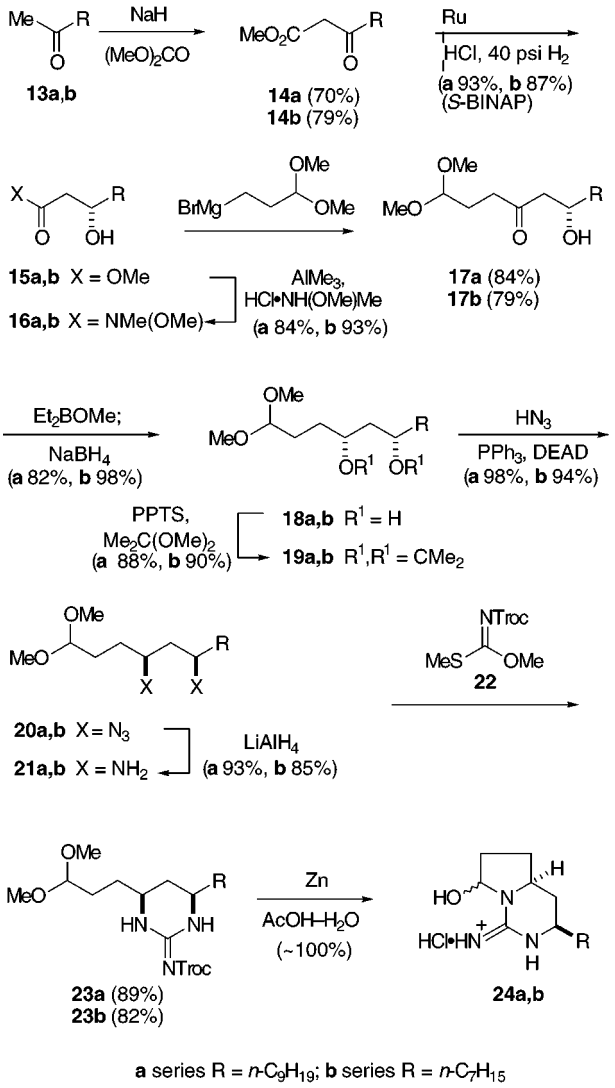
Scheme 1



Our initial exploratory studies were done with intermediates having an *n*-nonyl side chain, and thus, we began by acylation of 2-undecanone (**13a**)[18] with dimethyl carbonate to provide *β*-ketoester **14a** (Scheme 2).[19] Enantioselective reduction of this intermediate using a modification[20] of Noyori's procedure[17,21] provided *β*-hydroxyester **15a** in 93% yield and 95% ee.[22] Conversion of **15a**

(13) Stites, W. E. *Chem. Rev.* **1997**, *97*, 1233.
(14) A preliminary report of our asymmetric synthesis of **10** was disclosed in 1996: Franklin, A. S.; Overman, L. E. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL; American Chemical Society: Washington, DC, 1996; ORG 139.
(15) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235.
(16) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657.
(17) Noyori, R.; Ohkuma, T.; Kitamura, H.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
(18) Nakahata, M.; Imaida, M.; Ozaki, H.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2186.
(19) Garcia, D. M.; Yamada, H.; Hatakeyama, S.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 3325.

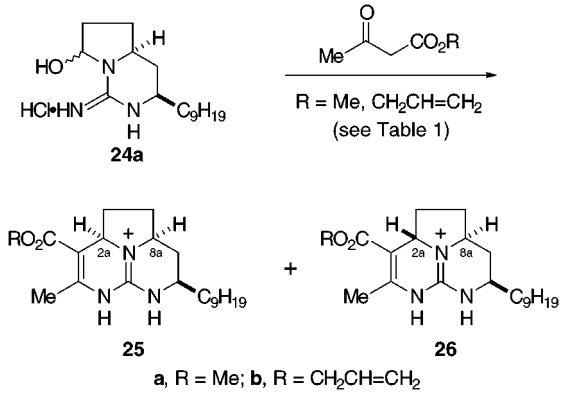
Scheme 2



to Weinreb amide[23] **16a**, followed by addition of 3,3-dimethoxypropylmagnesium bromide[24] afforded *β*-hydroxyketone **17a** in 71% overall yield. Syn-selective reduction of **17a** using diethylmethoxyborane and $NaBH_4$[25] gave 1,3-diol **18a** as a single diastereomer in 82% yield. The syn stereochemistry of **18a** was confirmed by formation of acetonide derivative **19a** whose ^{13}C NMR spectral data included diagnostic peaks at 98.3, 30.2, and 19.8.[26−28]

Following a recent report, we initially attempted to introduce the guanidine functionality by direct displacement of diol **18a** with bis-BOC-protected guanidine under Mitsunobu conditions.[29] Unexpectedly, this diol proved unreactive to this reagent combination. However, standard Mitsunobu displacement[30,31] of **18a** with hydrazoic acid,[32] followed by reduction of the resulting diazide **20a** with $LiAlH_4$, successfully delivered diamine **21a** in 91% overall yield from **18a**. Condensation of **21a** with carbonimidothioate **22**[33] in CH_2Cl_2 cleanly provided tetrahydropyrimidine **23a** in high yield. Use of MeOH as the reaction solvent in this condensation led to the corresponding guanidine methyl carbamate. The 2,2,2-trichloroethyl protecting group of **23a** was then cleaved using zinc and aqueous acetic acid to give the bicyclic hexahydropyrrolopyrimidinium chloride salt **24a**, after precipitation of zinc residues with H_2S and acidification with HCl. The ^1H and ^{13}C NMR spectra of crude **24a**, a 1:1 mixture of aminal epimers, were extremely clean and showed no evidence of a monocyclic guanidine−aldehyde tautomer or higher oligomers. This intermediate was used without further purification.

Scheme 3



Tethered Biginelli Cyclizations. Condensations of **24a** with allyl or methyl acetoacetate were examined under a variety of reaction conditions (Scheme 3, Table 1). Under all conditions examined, a mixture of two stereoisomeric esters, **25** and **26**, was formed in moderate to excellent yield. When typical Knoevenagel conditions (1 equiv of morpholinium acetate) were employed, the syn-2a,8a stereoisomer **25** predominated. Syn-stereoselectivity was quite solvent dependent and generally increased with increasing ionizing power of the solvent. Stereoselection was optimal in CF_3CH_2OH and could be further enhanced by decreasing the reaction temperature, reaching a maximum of 97:3 at room temperature (entries 1, 2, and 4). However, lowering the reaction temperature led to impractical reaction times, with over 1 week being required for complete consumption of **24a** at room temperature. The amine base employed had little effect on the diastereoselectivity, with morpholine and pyrrolidine giving similar product ratios in MeOH. In reactions performed in CF_3CH_2OH, small variations in the ratio of morpholine to acetic acid did not significantly alter the diastereoselectivity. When the tethered Biginelli condensation was carried out in the presence of an excess of a strong protic acid (entries 12−14), the anti-2a,8a tricyclic guanidine **26** predominated slightly. However, no conditions were found that provided **26** in satisfactory stereoselectivity.[34]

(20) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.
(21) Kitamura, M.; Sayo, N.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.
(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(23) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(24) Lee, T. V.; Porter, J. R. *Org. Synth.* **1995**, *72*, 189.
(25) Chen, K. M.; Hardmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(26) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
(27) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
(28) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
(29) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.
(30) Mitsunobu, O. *Synthesis* **1981**, 1.
(31) Hassner, A.; Dehaen, W. *J. Org. Chem.* **1990**, *55*, 2243.
(32) Hydrazoic acid was generated by the procedure reported in: Wolff, H. *Org. React.* **1946**, *3*, 327.
(33) Atkins, P. R.; Glue, S. E. J.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2644.

Table 1. Tethered Biginelli Condensation of 24a to Yield Tricyclic Guanidines 25 and 26

		reactions conditions[a]				tricyclic guanidine products	
entry	R	acid (1 equiv)	base (1 equiv)	solvent	T, °C	yield, %	**25**:**26**[c]
1	allyl	HOAc	morpholine	CF_3CH_2OH	rt	*b*	32:1
2	allyl	HOAc	morpholine	CF_3CH_2OH	40	*b*	20:1
3	allyl	HOAc	morpholine[d]	CF_3CH_2OH	90	*b*	9:1
4	Me	HOAc	morpholine	CF_3CH_2OH	90	80	6.5:1
5	allyl	HOAc	morpholine	EtOH	80	65	7.7:1
6	allyl	HOAc	morpholine	DMF	90	63	7.7:1
7	allyl	HOAc	morpholine	THF	66	80	5.7:1
8	allyl	HOAc	morpholine	cyclohexane	80	71	4.6:1
9	allyl	HOAc	morpholine	CH_3CN	80	71	4.3:1
10	allyl	HOAc	morpholine	$Cl(CH_2)_2Cl$	85	64	3.7:1
11	Me	HOAc	morpholine	$Cl(CH_2)_2Cl$	90	95	1.3:1
12	Me	HCl[e]	morpholine	$Cl(CH_2)_2Cl$	90	*b*	1:1.3
13	Me	CF_3CO_2H[f]	none	$Cl(CH_2)_2Cl$	90	*b*	1:1.4
14	Me	CF_3CO_2H[e]	morpholine	$Cl(CH_2)_2Cl$	90	*b*	1:1.5

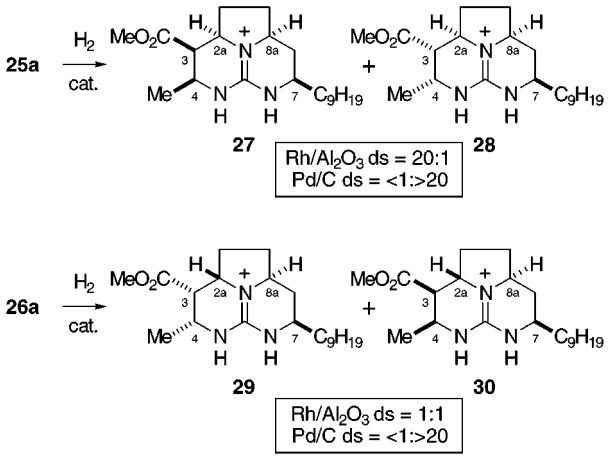
[a] **24a** (0.1−0.2 M), β-ketoester [R = Me (2 equiv); R = allyl (5 equiv)], Na_2SO_4 (3 equiv), reaction time typically 36 h. [b] Not determined. [c] Ratios were determined by ^{1}H NMR or HPLC analysis. [d] 2 equiv. [e] 10 equiv. [f] 5 equiv.

Separation of **25** and **26** proved difficult and pure samples were isolated only after extensive MPLC or HPLC purification. The structures of Biginelli products **25** and **26** were assigned on the basis of comparison of their NMR data with that of batzelladine B degradation product **10** and from ^{1}H NMR NOE data, where irradiation of H-8a led to enhancement of H-2a in syn isomer **25** but not in **26**.

Although not established experimentally in all cases, it is likely that products **25** and **26** do not interconvert under the reaction conditions reported in Table 1. For example, no equilibration of isomers was observed upon resubmission of a mixture of **25** and **26** enriched in the minor isomer to the conditions of entries 4, 11, and 13 of Table 1. Since little is known about the mechanism of the guanidine variant of the Biginelli condensation, a satisfactory rationale for the variation in stereochemical outcome with reaction conditions of the tethered Biginelli condensation of eq 1 cannot be advanced at this point.[35−37]

Hydrogenation Studies and Double-Pulsed Field Gradient Spin−Echo NOE Studies of the Decahydro-5,6,8b-triazaacenaphthalene Products. Since batzelladine alkaloids A (**1**), D (**4**), F (**6**), and G contain 4-methyl-7-alkyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthalene-3-carboxylic acid subunits, we investigated facial selectivity in the reduction of the potential octahydro precursors **25a** and **26a**. As first described by Snider,[9] hydrogenation of the **25a** in methanol in the presence of Rh on alumina results in selective addition of hydrogen from the α-face to provide **27** and **28** in a ∼20:1 ratio. Facial selectivity of hydrogenation of this syn precursor is highly dependent on the catalyst employed, with exclusive β-face addition to provide **28** (71% yield) being observed with Pd on carbon in methanol.[38]

Scheme 4



Hydrogenation of anti isomer **26a** in methanol using Pd/C as the catalyst proceeded from the face opposite the axial allylic C2a hydrogen to give **30** as the only observed product in 94% yield (Scheme 4). However, when Rh on alumina was employed as the catalyst in methanol, no selectivity was observed in the anti series and **29** and **30** were obtained in a 1:1 ratio (97% combined yield). Since natural batzelladine alkaloids having a decahydro-5,6,8b-triazaacenaphthalene-3-carboxylate fragment (**1**, **4**, **6**, and batzelladine G) are all believed to have the relative stereochemistry found in **29**, a variety of other hydrogenation catalysts and reaction conditions were surveyed in an attempt to optimize formation of **29**. Unfortunately, no wholly satisfactory solution has been found to date.[39] To minimize epimerization of the ester, which occasionally was a complication when this substituent was axial (i.e., with **27** and **30**), all hydrogenation reactions were performed in the presence of 1% formic acid.[9]

Isomerically pure samples of stereoisomeric decahydro products **29** and **30** were obtained by HPLC purification.

(34) It should be noted that an insoluble, though labile, intermediate of unknown structure is formed within 1 h when the Biginelli condensation of **24a** and allyl acetoacetate was performed in THF. Although this intermediate provided **25b** and **26b** when reexposed to the reaction conditions in both THF and trifluoroethanol, the diastereoselectivity of the trifluoroethanol reaction dropped below that of the reaction performed in THF.

(35) To our knowledge, mechanistic studies of the guanidine variant of the Biginelli condensation have not been reported.[36] Our initial investigations of stereochemical control in the tethered guanidine Biginelli condensation in simpler systems are described in an accompanying paper.[37]

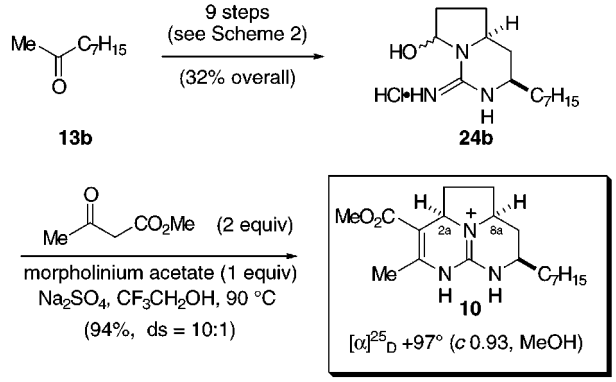
(36) For a recent mechanistic study of the classical Biginelli condensation of aldehydes, β-ketoesters, and urea in the presence of HCl, see: Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803.

(37) McDonald, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520.

(38) Snider, B. B. Personal communication to L.E.O., July 19, 1996.

(39) Reduction of **26** with a variety of heterogeneous hydrogenation catalysts such as PtO_2, Pd/Al_2O_3, Ru/C, Ru/Al_2O_3, and Rh/C in solvents such as MeOH and hexanes did not result in enhanced stereoselectivity in forming **29**. Asymmetric hydrogenation catalysts such as [(DUPHOS)-Rh(COD)]$^+$($^-$OTf) did not catalyze reduction of **26a**.[40]

Scheme 5



The stereochemistry of these isomers, which have not been previously described, as well as that of **27** and **28** was rigorously established by transient NOE build-up rates obtained using the double-pulsed field gradient spin−echo NOE (DPFGSE-NOE).[41,42] The DPFGSE-NOE method is notable for the clean, unambiguous spectra it produces, allowing small enhancements to be quantified accurately.

Absolute Stereochemistry of the Tricyclic Portion of Batzelladine B by Enantioselective Synthesis of Methanolysis Product 10. Following the sequence developed during our initial studies, 2-nonanone (**13b**)[18] was converted, by way of β-hydroxyester **17b** (96% ee),[22] to bicyclic Biginelli precursor **24b** (Scheme 2). This optimized sequence provided **24b** on a gram scale in nine steps and 32% overall yield from 2-nonanone. Condensation of this intermediate with 2 equiv of methyl acetoacetate in the presence of 1 equiv of morpholinium acetate and excess Na_2SO_4 in CF_3CH_2OH at 90 °C delivered tricyclic guanidine methyl ester **10** and the corresponding trans stereoisomer in a 10:1 ratio and 94% combined yield (Scheme 5). Purification of this mixture by reversed-phase HPLC provided isomerically pure **10** in 82% yield. Synthetic **10** showed ^{1}H and ^{13}C NMR, IR, and HRMS consistent with those reported for this derivative of batzelladine B[2] and for the corresponding synthetic racemate.[9] Pure synthetic **10** showed $[\alpha]^{25}_D$ +97 (c = 0.93, MeOH), while $[\alpha]^{25}_D$ +121 (c = 0.93, MeOH) has been reported for this degradation product of batzelladine B.[2,43]

Conclusion

Tethered Biginelli condensation of enantioenriched hexahydropyrrolopyrimidines **8** with β-ketoesters provides efficient asymmetric access to tricyclic guanidines **9** having a syn relationship of the angular C2a and C8a hydrogens (eq 1). This sequence provides the first practical enantioselective access to this fragment of batzelladine alkaloids B (**2**) and E (**5**). The efficiency of this strategy is illustrated in the synthesis of the dextrorotatory enantiomer of batzelladine B methanolysis product **10** in 10 steps and 25% overall yield from 2-nonanone and methyl acetoacetate. The asymmetric synthesis of **10** documented here establishes, for the first time, that the absolute configuration of the tricyclic portion of batzelladine B (**2**) is 25a*R*,28*S*,30*R*. The 4-methyl-7-alkyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthalene-3-carboxylic acid subunit, e.g., **29**, of batzelladine alkaloids A (**1**), D (**4**), F (**6**), and G was also prepared for the first time. However, low stereoselectivity in the tethered Biginelli condensation and in the subsequent hydrogenation step require that further improvements in the synthetic sequence to be realized before practical access to this latter tricyclic fragment of the batzelladine alkaloids is achieved.[44]

Experimental Section[45]

Methyl 3-Oxodecanoate (14b).[18] Dimethyl carbonate (85 mL, 1.0 mol) was added to a solution of NaH (44 g of a 60% dispersion in mineral oil, 1.1 mol) and Et_2O (100 mL) at room temperature. The resulting mixture was stirred and heated at reflux, while 2-nonanone (**13b**, 85.5 mL, 0.50 mol) was added dropwise over 3 h. Additional Et_2O (175 mL total) was added portionwise over the next 6 h. After ~2 h, the heterogeneous reaction mixture could no longer be stirred, and this brown mass was heated in a 75 °C oil bath for 21 h. The mixture was cooled to 0 °C and carefully partitioned between Et_2O−MeOH (4:1, 500 mL) and 1 M HCl (500 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 500 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (500 mL), dried ($MgSO_4$), and concentrated to a dark yellow oil. The residue was purified by distillation under reduced pressure (bp 90 °C, 1 mm) to give 71 g (79%) of the known β-ketoester **14b**[46] as a colorless oil that solidified below 10 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.86 (s, 0.1H), 3.60 (s, 2.9H), 3.53 (s, 0.1H), 3.34 (s, 2H), 2.42 (t, J = 7.3 Hz, 1.8H), 2.08 (m, 0.2 H), 1.46 (t, J = 6.7 Hz, 2H), 1.16 (broad s, 8H), 0.75 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 202.5, 178.8, 172.7, 170.0, 167.4, 88.3, 59.3, 51.9, 51.0, 50.7, 48.6, 43.4, 42.7, 34.7, 31.4, 31.2, 28.7, 28.7, 28.9, 27.9, 27.1, 26.0, 23.1, 22.3, 13.7 ppm; IR (film) 1749, 1717, cm^{-1}; MS (CI) m/z 201.1495 (201.1490 calcd for $C_{11}H_{21}O_3$, MH), 169, 158, 127.

Methyl (3*S*)-Hydroxydecanoate (15b). (*S*)-BINAP−$RuCl_2$ (128 mg, 0.082 mmol) and HCl (1.0 mL of a 1 M solution in MeOH) were added to a solution of β-ketoester **14b** (30.0 g, 0.15 mol) and MeOH (66 mL) that was sparged with N_2.[20,21] The vessel was evacuated and refilled with N_2 (3×) and then H_2 (3×), and the pressure was maintained at 40 psi. The reaction was then heated to 40 °C with vigorous stirring for 6 h. The reaction was allowed to cool to room temperature and concentrated to give a dark orange oil. This residue was distilled under reduced pressure (bp 100 °C, 0.3 mm) to give 26.0 g (87%) of alcohol **15b** as a colorless oil that solidified below 10 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96 (broad m, 1H), 3.67 (s, 3H), 2.91 (broad s, 1H), 2.48 (dd, J = 16.3, 3.4 Hz, 1H), 2.37 (dd, J = 16.3, 8.8 Hz, 1H), 1.50−1.33 (m, 2H), 1.24 (broad s, 10H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.4, 67.9, 51.6, 41.1, 36.5, 31.7, 29.4, 29.1, 25.4, 22.6, 14.0 ppm; IR (film) 3458, 1740 cm^{-1}; MS (CI) m/z 203.1650 (203.1647 calcd for $C_{11}H_{23}O_3$, MH), 203, 185, 171, 153; $[\alpha]^{24}_D$ = +16.4, $[\alpha]^{24}_{577}$ = +18.3, $[\alpha]^{24}_{546}$ = +20.0, $[\alpha]^{24}_{435}$ = +35.1, $[\alpha]^{24}_{405}$ = +40.2 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.18; H, 10.87.

(40) (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (b) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142.

(41) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J *J. Am. Chem. Soc.* **1995**, *117*, 4199.

(42) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302.

(43) Since the counterion of **10** derived from natural batzelladine A is not described, the significance, if any, of this 30% discrepancy in rotation magnitude is unknown.

(44) An improved route to the 2a,8a-anti series employing an alternate tethered Biginelli construction of the 4,7-disubstituted-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium-3-carboxylate unit has been developed: Ly, S. K.; Overman, L. E. To be submitted for publication.

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

(46) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.

(3*S*)-Hydroxy-*N*-methoxy-*N*-methyldecanamide (16b). Following the general conditions of Weinreb,[23] Me_3Al (56 mL of a 2.0 M solution in toluene, 0.11 mol) was added dropwise to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (12.1 g, 0.12 mol) and toluene (150 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, at which time a homogeneous solution was formed, after 15 min re-cooled to 0 °C, and a solution of the ester **15b** (6.52 g, 0.03 mol) and toluene (90 mL) was then added via cannula. The reaction was allowed to warm to room temperature over 1 h and then quenched with aqueous 2 M tartaric acid (750 mL). The resultant biphasic mixture was stirred vigorously for 1.5 h, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 300 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to provide a light yellow oil. This crude oil was purified by flash column chromatography (3:2 hexanes−EtOAc) to give 6.40 g (93%) of amide **16b** as a pale yellow oil which solidified below 10 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93−3.88 (broad m, 1H), 3.83−3.77 (broad m, 1H), 3.59 (s, 3H), 3.09 (s, 3H), 2.54 (broad d, J = 16.5 Hz, 1H), 2.35 (dd, J = 16.5, 9.5 Hz, 1H), 1.46−1.27 (m, 2H), 1.18 (broad s, 10H), 0.77 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.6, 67.6, 60.9, 38.0, 36.4, 31.6, 29.3, 29.0, 25.3, 22.4, 13.9 ppm; IR (film) 3450, 1643 cm^{-1}; MS (CI) *m*/*z* 232.1913 (232.1912 calcd for $C_{12}H_{26}NO_3$, MH); $[\alpha]^{24}_D$ = +39.3, $[\alpha]^{24}_{577}$ = +42.3, $[\alpha]^{24}_{546}$ = +48.4, $[\alpha]^{24}_{435}$ = +82.5, $[\alpha]^{24}_{405}$ = +98.8 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{12}H_{25}NO_3$: C, 62.30; H, 10.89; N, 6.05. Found: C, 62.02; H, 10.84; N, 5.89.

(6*S*)-Hydroxy-1,1-dimethoxy-4-tridecanone (17b). Following the procedure of Lee and Porter,[24] 3-bromopropionaldehyde dimethoxyacetal (21.4 mL, 0.16 mol) was added dropwise over 2.5 h to a solution of Mg (5.16 g, 0.21 mol), I_2 (330 mg, 1.4 mmol), and THF (170 mL) using an external water bath to maintain the reaction temperature at 25 °C. After the addition, the resultant dark gray suspension was stirred for 1 h and used without further purification.

A solution of amide **16b** (4.63 g, 20.0 mmol) and THF (100 mL) at 0 °C was treated dropwise with freshly prepared 3,3-dimethoxypropylmagnesium bromide (185 mL of a ∼0.5 M solution in THF, ∼150 mmol). The reaction was allowed to warm to room temperature for 2 h. After 30 min at room temperature, the yellow-green mixture was then partitioned with saturated aqueous $NaHCO_3$ (250 mL) and Et_2O (200 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 200 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to a light yellow oil. The crude oil was purified by flash column chromatography (70:30:1 hexanes−EtOAc−Et_3N) to give 4.30 g (79%) of ketone **17b** as a colorless oil that solidified below 10 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.29 (app t, J = 5.4, 1H), 4.97−3.95 (broad m, 1H), 3.24 (s, 6H), 3.12 (broad s, 1H), 2.51−2.42 (m, 4H), 1.82 (app dt, J = 13.9, 5.8, 2H), 1.44−1.28 (m, 2H), 1.20 (broad s, 10H,), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 211.1, 103.6, 67.6, 53.1, 49.2, 37.9, 36.4, 31.7, 29.4, 29.1, 26.2, 25.3, 22.5, 13.9 ppm; IR (film) 3472, 1713 cm^{-1}; MS (CI) *m*/*z* 243.1972 (243.1960 calcd for $C_{14}H_{27}O_3$, M − OMe), 243, 225, 211, 193, 153, 143; $[\alpha]^{24}_D$ = +5.7, $[\alpha]^{24}_{577}$ = +7.0, $[\alpha]^{24}_{546}$ = +8.0, $[\alpha]^{24}_{435}$ = +13.5, $[\alpha]^{24}_{405}$ = +15.1 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.49; H, 10.91.

(4*R*,6*S*)-1,1-Dimethoxytridecane-4,6-diol (18b). Following the general conditions of Chen and co-workers,[25] diethylmethoxyborane (12.4 mL of a 1.0 M solution in THF, 12.4 mmol) was added to a solution of β-hydroxyketone **17b** (3.10 g, 11.3 mmol), MeOH (33 mL), and THF (130 mL) at −78 °C. The reaction was maintained at −78 °C for 30 min, and then $NaBH_4$ (840 mg, 22 mmol) was added slowly. After 1 h at −78 °C, MeOH pH 7 buffer (1:1, 200 mL) was added, and the quenched reaction was allowed to warm to room temperature. The resultant biphasic solution was then cooled to 0 °C, and H_2O_2 (30% aqueous, 12 mL) was added dropwise. After 1 h at room temperature, H_2O (90 mL) was then added, and the phases were separated. The aqueous phase was then extracted with Et_2O (3 × 500 mL). The combined organic layers were dried (K_2CO_3) and concentrated to a light yellow oil. This oil was purified by flash column chromatography (60:40:1 hexanes−EtOAc−Et_3N) to give 3.06 g (98%) of diol **18b** as a colorless oil that solidified below 10 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.31 (app t, J = 5.5 Hz, 1H), 4.09 (broad s, 1H), 3.88 (broad s, 1H), 3.76−3.75 (broad m, 2H), 3.26 (s, 3H), 3.25 (s, 3H), 1.69−1.59 (m, 2H), 1.51−1.32 (m, 6H), 1.21 (broad s, 10H), 0.81 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 104.5, 72.6, 72.3, 52.9, 52.6, 42.6, 38.0, 32.7, 31.7, 29.5, 29.1, 28.4, 25.3, 22.5, 14.0 ppm; IR (film) 3452 cm^{-1}; $[\alpha]^{24}_D$ = +1.9, $[\alpha]^{24}_{577}$ = +2.5, $[\alpha]^{24}_{546}$ = +3.0, $[\alpha]^{24}_{435}$ = +5.5, $[\alpha]^{24}_{405}$ = +6.7 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{32}O_4$: C, 65.18; H, 11.67. Found: C, 65.10; H, 11.74.

(4*S*,6*R*)-1,1-Dimethoxytridecan-4,6-diazide (20b). Hydrazoic acid (46 mL of a 1.0 M solution in toluene, 46 mmol)[32] was added dropwise to a solution of diol **18b** (3.00 g, 10.9 mmol), Ph_3P (11.5 g, 44.0 mmol), and THF (150 mL) at 0 °C. Diethyl azodicarboxylate (6.8 mL, 43 mmol) was then added dropwise over 2 h. The resulting pale orange mixture was allowed to warm to room temperature for 1 h and then was quenched with H_2O (1 mL). The reaction was concentrated to a dark yellow mixture, and this residue was purified by flash column chromatography (90:10:1 hexanes−EtOAc−Et_3N) to give 3.34 g (94%) of diazide **20b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.36 (app t, J = 5.3 Hz, 1H), 3.43−3.34 (m, 2H), 3.31 (s, 6H), 1.77−1.34 (m, 8H), 1.27 (broad s, 10H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 103.9, 59.6, 59.5, 53.0, 52.7, 38.6, 34.1, 31.6, 29.2, 29.1, 28.8, 28.7, 25.8, 22.5, 14.0 ppm; IR (film) 2103 cm^{-1}; $[\alpha]^{24}_D$ = −7.2, $[\alpha]^{24}_{577}$ = −6.5, $[\alpha]^{24}_{546}$ = −8.1, $[\alpha]^{24}_{435}$ = −12.0, $[\alpha]^{24}_{405}$ = −14.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{30}N_6O_2$: C, 55.19; H, 9.26; N, 25.74. Found: C, 55.05; H, 9.31; N, 25.61.

(4*S*,6*R*)-1,1-Dimethoxytridecane-4,6-diamine (21b). Lithium aluminum hydride (29 mL of a 1.0 M solution in THF, 29 mmol) was added dropwise to a solution of diazide **20b** (3.1 g, 9.5 mmol) and THF (100 mL) at 0 °C. The reaction was then allowed to warm to room temperature and maintained for 4 h at 0 °C. Subsequently, NaF (4.8 g, 114 mmol), H_2O (1.5 mL, 87 mmol), and THF (200 mL) were added, and the resultant slurry was stirred vigorously for 16 h. The reaction was then filtered and the resulting filtrate concentrated to give 2.21 g (85%) of diamine **21b** as a colorless oil that was used without any purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.21 (app t, J = 5.6 Hz, 1H), 3.17 (s, 3H), 3.16 (s, 3H), 2.71−2.64 (m, 2H), 1.57−1.22 (m, 8H), 1.25 (broad s, 10H), 0.78 (t, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 104.3, 52.5, 52.2, 49.9, 49.7, 45.8, 38.9, 33.5, 31.5, 29.4, 29.0, 28.6, 25.6, 22.3, 13.8 ppm; IR (film) 3366, 3286 cm^{-1}; MS (CI) *m*/*z* 275.2695 (275.2698 calcd for $C_{15}H_{35}N_2O_2$, MH), 285, 275, 253, 242, 211, 194, 167, 154, 128; $[\alpha]^{24}_D$ = −0.2, $[\alpha]^{24}_{577}$ = +1.1, $[\alpha]^{24}_{546}$ = −1.3, $[\alpha]^{24}_{435}$ = +1.8, $[\alpha]^{24}_{405}$ = +2.3 (*c* 1.0, $CHCl_3$).

(4*S*,6*R*)-2-(2,2,2-Trichloroethoxycarbonylimino)-4-(3,3-dimethoxypropyl)-6-heptyl-3,4,5,6-tetrahydropyrimidine (23b). Following the general procedures of Kay and co-workers,[33] a solution of diamine **21b** (2.2 g, 8.02 mmol), carbonimidothioate **22** (2.5 g, 8.8 mmol), and CH_2Cl_2 (100 mL) was maintained at room temperature for 19 h. The reaction was concentrated, and the residue was purified by flash column chromatography (100:1 hexanes−Et_3N and then 90:10:1 hexanes−*i*-PrOH−Et_3N) to give 3.10 g (82%) of guanidine **23b** as a pale yellow oil that formed a white wax on standing at 0 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78−7.71 (broad m, 2H), 4.64 (s, 2H), 4.27 (app t, J = 4.5 Hz, 1H), 3.58−3.33 (m, 2H), 3.26 (s, 6H), 1.98−1.93 (m, 1H), 1.59−1.44 (m, 7H), 1.21 (broad s, 10H), 0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 161.6, 158.9, 103.9, 96.1, 74.4, 53.0, 52.8, 49.5, 49.3, 35.4, 33.3, 31.5, 30.1, 29.2, 28.9, 27.9, 24.9, 22.4, 13.9 ppm; IR (film) 3285, 1631, 1560 cm^{-1}; MS (FAB) *m*/*z* 474.1697 (474.1693 calcd for $C_{19}H_{35}N_3O_4Cl_3$, MH), 442, 410, 326, 300, 262, 194, 154, 136; $[\alpha]^{24}_D$ = −0.7, $[\alpha]^{24}_{577}$ = +0.0, $[\alpha]^{24}_{546}$ = +0.3, $[\alpha]^{24}_{435}$ = +0.8, $[\alpha]^{24}_{405}$ = −0.2 (*c* 1.0, $CHCl_3$).

(3*R*,4a*S*)-1-Imino-7-hydroxy-3-heptyl-2,3,4,4a,5,6,7-octahydropyrrolo[1,2-*c*]-pyridinium Chloride (24b). Zinc dust (2.52 g, 38.5 mmol) was added to a solution of the protected guanidine **23b** (1.00 g, 2.11 mmol), glacial acetic acid (30 mL), and water (30 mL) at room temperature. After 3 h,

the mixture was filtered, and the filtrate was saturated with H_2S. The resulting white precipitated Zn salts were removed by filtration through a Celite pad. The filtrate was then treated with HCl (1 N aqueous, 2.4 mL, 2.4 mmol) and was concentrated. This light yellow residue was diluted in CH_2Cl_2 (50 mL) and filtered to remove the remaining Zn salts. The filtrate was concentrated to give 620 mg (100%) of deprotected guanidine **5** as a 1:1 mixture of diastereoisomers. This light yellow oil was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (app broad d, J = 39.6 Hz, 1H), 6.53 (m, 1H), 5.55 (d, J = 16.6 Hz, 1H), 3.88 (m, 1H), 3.43−3.35 (m, 2H), 2.29−1.98 (m, 4H), 1.66−1.25 (broad m, 4H), 1.22 (broad s, 10H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 152.9, 152.6, 82.6, 81.0, 57.3, 55.0, 51.2, 50.4, 35.2, 35.1, 33.7, 33.5, 33.0, 32.7, 31.8, 29.9, 29.5, 29.4, 29.3, 29.2, 29.1, 25.3, 25.2, 22.6, 14.0 ppm; IR (film) 3311, 1652, 1622 cm^{-1}; MS (FAB) *m*/*z* 235.2045 (235.2048 calcd for $C_{14}H_{25}N_3$, M − H_2O), 410, 300, 262, 222, 194, 154, 136; $[\alpha]^{24}_D$ = −27.6, $[\alpha]^{24}_{577}$ = −30.1, $[\alpha]^{24}_{546}$ = −34.3, $[\alpha]^{24}_{435}$ = −58.6, $[\alpha]^{24}_{405}$ = −70.6 (*c* 1.0, $CHCl_3$).

Methyl (2a*R*,7*R*,8a*S*)-7-Heptyl-4-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylenium-3-carboxylate (10). A solution of guanidine **24b** (0.612 mg, 2.11 mmol), morpholine (0.18 mL, 2.3 mmol), glacial acetic acid (0.13 mL, 2.2 mmol), methyl acetoacetate (0.45 mL, 4.2 mmol), Na_2SO_4 (900 mg, 6.33 mmol), and 1,1,1-trifluoroethanol (5 mL) was heated to reflux for 36 h. The dark yellow reaction mixture was concentrated and purified by flash column chromatography (80:20:1 hexanes−*i*-PrOH−AcOH) to give 730 mg (94%) of a 10:1 mixture of **10** and its C-2a epimer as a yellow oil. A 100 mg portion of this sample was separated by preparative HPLC (5 μm Alltima reversed-phase C18 silica, 18:10:0.1 CH_3CN-H_2O−TFA) to give isomerically pure tricyclic guanidine **10** (82 mg, 82%) and 7 mg (7%) of the corresponding C2a epimer. Guanidine **10**: $[\alpha]^{24}_D$ = +97.2, $[\alpha]^{24}_{577}$ = +104, $[\alpha]^{24}_{546}$ = +119, $[\alpha]^{24}_{435}$ = +221, $[\alpha]^{24}_{405}$ = +277 (*c* 0.93, CH_3OH), showed ^{1}H and ^{13}C NMR in accord with reported data.[2,9]

Biginelli Condensation of 24a with Methyl Acetoacetate in Dichloroethane To Form Tricyclic Guanidines 25a and 26a. A solution of **24a** (367 mg, 1.15 mmol), morpholine (101 μL, 1.16 mmol), acetic acid (66 μL, 1.2 mmol), methyl acetoacetate (0.25 mL, 2.3 mmol), Na_2SO_4 (492 mg, 3.46 mmol), and 1,2-dichloroethane (5 mL) was heated at reflux for 36 h. The reaction was concentrated, and the residue was purified by flash column chromatography (80:20:1 hexanes−*i*-PrOH−AcOH) to give 436 mg (95%) of a 1.3:1 mixture of **25a** and **26a** as a yellow oil. These epimers were separated by preparative HPLC (5 μm Alltima silica, 97:3:0.5 CH_2Cl_2−MeOH−AcOH) to give pure samples of both isomers. **25a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.46−4.37 (m, 1H), 3.73 (s, 3H), 3.73−3.65 (m, 1H), 3.49−3.33 (m, 1H), 2.60−2.47 (m, 1H), 2.42−2.28 (m, 1H), 2.35 (s, 3H), 2.20−2.10 (m, 1H), 2.10−1.16 (m, 19H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 165.3, 146.2, 144.4, 100.5, 57.0, 55.6, 51.3, 50.1, 33.4, 33.0, 32.9, 31.7, 29.3, 29.1, 26.7, 25.0, 22.5, 17.5, 14.0 ppm; IR (film) 3228, 1694, 1591 cm^{-1}; MS (FAB) *m*/*z* 362.2813 (362.2807 calcd for $C_{21}H_{36}N_3O_2$, MH), 149; $[\alpha]^{24}_D$ = +95.2, $[\alpha]^{24}_{577}$ = +103.9, $[\alpha]^{24}_{546}$ =+117.6, $[\alpha]^{24}_{435}$ = +142.3, $[\alpha]^{24}_{405}$ = +48.5 (*c* 1.0, MeOH). **26a:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (dd, J = 11.0, 4.2 Hz, 1H), 3.71−3.60 (m, 1H), 3.70 (s, 3H), 3.51−3.44 (m, 1H), 2.63 (app dt, J = 12.4, 5.2 Hz, 1H), 2.36−2.27 (m, 1H), 2.33 (s, 3H), 1.88 (ddd, J = 23.4, 11.5, 5.5 Hz, 1H), 1.80−1.16 (m, 19H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 165.3, 149.1, 148.2, 103.4, 55.3, 54.4, 52.0, 51.0, 34.8, 32.8, 31.8, 31.7, 29.4, 29.3, 29.2, 25.3, 22.6, 17.6, 14.0 ppm; IR (film) 3218, 1694 cm^{-1}; MS (FAB) *m*/*z* 362.2802 (362.2807 calcd for $C_{21}H_{36}N_3O_2$, MH), 149; $[\alpha]^{24}_D$ = +16.5, $[\alpha]^{24}_{577}$ = +16.1, $[\alpha]^{24}_{546}$ = +20.7, $[\alpha]^{24}_{435}$ = +65.1, $[\alpha]^{24}_{405}$ = +96.3 (*c* 1.0, MeOH).

Hydrogenation of 26a with Rh/Al_2O_3 in Methanol. Preparation of Methyl (2a*R*,3*S*,4*R*,7*R*,8a*S*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride-3-carboxylate (29) and Methyl (2a*R*,3*R*,4*S*,7*R*,8a*S*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride-3-carboxylate (30). A solution of **26a** (50 mg, 0.14 mmol), formic acid (88%, 100 μL), and MeOH (10 mL) was stirred vigorously under 50 psi of H_2 in the presence of 5% Rh/Al_2O_3 (245 mg, 0.120 mmol) for 18 h. The reaction was filtered through a Celite pad, and the filtrate was concentrated to give 45 mg (90%) of a 1:1 mixture of **29** and **30** as a colorless oil. This mixture was purified by preparative HPLC (5 μm Alltima reversed-phase C18 silica, 20:10:0.1 CH_3CN-H_2O−TFA) to give 20 mg (45%) of **29** and 19 mg (42%) of **30**, both as colorless oils. **29**: ^{1}H NMR (CD_3OD, 500 MHz) δ 3.95−3.92 (m, 1H), 3.85−3.82 (m, 1H), 3.7−3.74 (dd, J = 10.9, 7.6 Hz, 1H), 3.71 (s, 3H), 3.56−3.52 (m, 1H), 3.15 (t, J = 4.0 Hz, 1H), 2.35−2.89 (m, 1H), 2.24−2.17 (m, 2H), 1.76−1.41 (m, 4H), 1.28 (broad s, 14H), 1.25 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 6.4 Hz, 3H); DPFGSENOE enhancements observed between H-2a and H-3 (strong), H-2a and H-4 (strong), H-2a and H-8a (weak), H-3 and H-2a (strong), H-3 and H-4 (strong), H-3 and H-8a (weak), H-8a and H-2a (weak); ^{13}C NMR (CD_3OD, 125 MHz) 171.1, 151.4, 57.7, 57.2, 53.1, 49.3, 45.3, 36.8, 34.1, 33.0, 31.4, (30.6, 30.5, 30.4), 29.3, 26.1, 23.6, 18.3, 14.4 ppm; IR (film) 3260, 1732, 1682, 1644 cm^{-1}; MS (FAB) *m*/*z* 350.2801 (364.2977 calcd for $C_{21}H_{38}N_3O_2$, MH), 327, 281, 221, 207, 191, 147, 136. **30**: ^{1}H NMR (CD_3OD, 500 MHz) δ 4.10−4.02 (m, 1H), 3.84−3.72 (m, 1H), 3.74 (s, 3H), 3.72−3.57 (m, 1H), 3.57−3.43 (m, 1H), 2.94 (dd, J = 10.8, 5.8 Hz, 1H), 2.48−2.41 (m, 1H), 2.23−2.28 (m, 1H), 2.24−2.20 (m, 1H), 1.71−1.17 (m, 19H), 1.14 (d, J = 6.5 Hz, 3H), 0.89 (t, J = 6.4 Hz, 3H); DPFGSE-NOE enhancements observed between H-2a and 4-CH_3 (strong), H-3 and H-4 (strong), H-3 and 4-CH_3 (medium), H-3 and H-6 (medium), H-4 and H-3 (strong), H-4 and 4-CH_3 (strong), 4-CH_3 and H-2a (strong), 4-CH_3 and H-4 (medium), H-7 and H-8a (medium), H-8a and H-2a (strong), H-8a and H-3 (strong); ^{13}C NMR (CD_3OD, 75 MHz) 171.0, 151.0, 57.1, 53.2, 52.9, 52.6, 36.8, 34.1, 33.0, 31.5, 30.6, 30.4, 26.2, 23.7, 19.6, 14.4 ppm; IR (film) 3266, 1732, 1651 cm^{-1}; MS (FAB) *m*/*z* 364.2974 (364.2964 calcd for $C_{21}H_{38}N_3O_2$, MH), 304.

Stereoselective Preparation of 30 by Hydrogenation of 26a with Pd/C in Methanol. A solution of **26a** (23 mg, 0.058 mmol), formic acid (88%, 50 μL), and MeOH (5 mL) was stirred vigorously under 50 psi of H_2 in the presence of 10% Pd/C (63 mg, 0.059 mmol) for 18 h. The reaction was filtered through a Celite pad, and the filtrate was concentrated to give 22 mg (94%) of essentially isomerically pure **30**.

Hydrogenation of 25a with Pd/C in Methanol. Preparation of Methyl (2a*S*,3*S*,4*R*,7*R*,8a*S*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride-3-carboxylate (28). A solution of **25a** (29 mg, 0.073 mmol), formic acid (88%, 50 μL), and MeOH (5 mL) was stirred vigorously under 50 psi of H_2 in the presence of Pd/C (10%, 77 mg, 0.072 mmol) for 18 h. The reaction was filtered through a Celite pad, and the filtrate was concentrated to give 21 mg (71%) of isomerically pure **28** as a colorless oil: ^{1}H NMR (CD_3OD, 300 MHz) δ 4.04−3.90 (m, 2H), 3.87−3.76 (m, 1H), 3.75 (s, 3H), 3.51−3.39 (m, 1H), 2.86 (dd, J = 11.3, 4.6 Hz, 1H), 2.41−2.17 (m, 3H), 1.80−1.21 (m, 19H), 1.13 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 6.6 Hz, 3H); DPFGSE-NOE enhancements observed between H-2a and H-3 (strong), H-2a and H-4 (strong), H-2a and H-8a (strong), H-3 and H-2a (strong), H-3 and H-4 (strong), H-3 and H-8a (weak), H-7 and H-8a (strong), H-8a and H-2a (medium); ^{13}C NMR (CD_3OD, 75 MHz) 171.2, 150.2, 57.3, 54.6, 52.9, 51.6, 35.9, 34.4, 33.0, 31.0, 30.6, 30.4, 30.3, 26.2, 23.7, 18.0, 14.4 ppm; IR (film) 3441, 1731, 1651 cm^{-1}; MS (FAB) *m*/*z* 364.2968 (364.2964 calcd for $C_{21}H_{38}N_3O_2$, MH), 304.

Hydrogenation of 25a with Rh/Al_2O_3 in Methanol. Preparation of Methyl (2a*S*,3*R*,4*S*,7*R*,8a*S*)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthylenium chloride-3-carboxylate (27). A solution of **25a** (21 mg, 0.053 mmol), formic acid (88%, 50 μL), and MeOH (5 mL) was stirred vigorously under 50 psi of H_2 in the presence of Rh/Al_2O_3 (5%, 130 mg, 0.063 mmol) for 18 h. The reaction was filtered through a Celite pad, and the filtrate was concentrated to give 21 mg (99%) of a 20:1 mixture of **27** and **28** as a colorless oil: ^{1}H NMR (CD_3OD, 300 MHz) δ 4.07−4.00 (m, 1H), 3.86−3.70 (m, 2H), 3.71 (s, 3H), 3.49−3.38 (m, 1H), 3.10 (app t, J = 4.2 Hz, 1H), 2.29−2.13 (m, 3H), 1.88−

1.70 (m, 1H), 1.71−1.17 (m, 18H), 1.25 (d, J = 6.7 Hz, 3H), 0.89 (t, J = 6.4 Hz, 3H); DPFGSENOE enhancements observed between H-2a and H-2 (strong), H-2a and 4-CH_3 (strong), H-2a and H-8a (weak), H-3 and H-4 (strong), H-4 and H-2a (weak), H-4 and H-3 (medium), H-4 and 4-CH_3 (strong), 4-CH_3 and H-2a (strong), 4-CH_3 and H-3 (medium), 4-CH_3 and H-4 (strong), H-7 and H-8a (strong), H-8a and H-2a (strong), H-8a and H-7 (strong); ^{13}C NMR (CD_3OD, 75 MHz) 171.2, 151.9, 58.8, 57.9, 52.9, 52.3, 51.6, 45.4, 35.9, 34.3, 33.0, 31.1, 31.0, 30.6, 30.4, 28.0, 26.2, 23.7, 17.9, 14.4 ppm; IR (film) 3269, 1731, 1633 cm^{-1}; MS (FAB) m/z 364.2972 (364.2964 calcd for $C_{21}H_{38}N_3O_2$, MH), 304.

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Supporting Information Available: Preparation and characterization data for the Mosher ester of **15b** and compounds **19b**, **25b** and **26b**; characterization data for the **a** series reported in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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