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 enantiomerically pure hexahydropropyropyrimidines \( B \) with \( \beta \)-ketosteres 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 methanolation 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 \( 25aR,28S,30R \). The 4-methyl-7-alkyl-1,2,3a,4,5,6,7,8,8a-decahydro-5,6,8b-triazaacenaphthalenes, \( 3 \), and \( 4 \), having the \( 2a,8a \)-anti stereochemistry.

Introduction

Batzelladines \( A \)–\( I \), along with other known guanidine alkaloids such as ptilocaullin, ptilomycin A \( (7) \), and crambescins \( A \) \( (3) \), \( 800 \) and \( 816 \), were isolated by Patil, Faulkner, and co-workers from the Caribbean sponge Batzella sp. \( 1 \). The batzelladine alkaloids are members of a growing class of guanidine alkaloids that exhibit a broad spectrum of biological activity. \( 5 \) 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. \( 1 \) Batzelladines \( F \) \( (6) \) and \( G \) induce dissociation of the complex of protein tyrosine kinase \( p56lck \) with CD4. \( 3 \) Since this association has been reported to deliver the tricyclic guanidine products in racemic form, \( 9 \) the stereochemistry of the tricyclic portions 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 \( ( \text{decahydro-5,6,8b-triazaacenaphthalene} ) \) ring system of the batzelladine alkaloids is also found in pentacyclic guanidine alkaloids of the crambescin/ptilomycin A \( (7) \) families. \( 8 \) 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 pyrroldine nitrogen.

In 1996, Snider and Chen using a presumed biomimetic strategy described constructions of tricyclic degradation products of several batzelladine alkaloids. \( 8 \) 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 decaldehyde-5,6,8b-triazaacenaphthalene ring systems through condensation of a dienedione with an amidine or guanidine unit, although beautifully concise, provide the tricyclic guanidine products in racemic form. \( 9 \) 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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(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. Recent model studies of Murphy \( 13 \) 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. The tricyclic guanidine \( ( \text{decahydro-5,6,8b-triazaacenaphthalene} ) \) ring system of the batzelladine alkaloids is also found in pentacyclic guanidine alkaloids of the crambescin/ptilomycin A \( (7) \) families. 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 pyrroldine nitrogen.


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

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). This latter enantioselective synthesis establishes that the absolute configuration of the tricyclic portion of batzelladine B (2) is as depicted in Figure 1.14

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). Enantioselective reduction of this intermediate using a modification20 of Noyori’s procedure21 provided β-hydroxyester 15a in 93% yield and 95% ee.22 Conversion of 15a

Figure 1. Representative alkaloids isolated from Batzella sp.

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(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.
Scheme 2

Scheme 3

to Weinreb amide\textsuperscript{23} \textit{16a}, followed by addition of 3,3-dimethoxypropylmagnesium bromide\textsuperscript{24} afforded \( \beta \)-hydroxyketone \textit{17a} in 71\% overall yield. Syn-selective reduction of \textit{17a} using diethylmethoxyborane and NaBH\textsubscript{4}\textsuperscript{25} gave 1,3-diol \textit{18a} as a single diastereomer in 82\% yield. The syn stereochemistry of \textit{18a} was confirmed by formation of an acetone derivative \textit{19a} whose \(^{13}\)C NMR spectral data included diagnostic peaks at 98.3, 30.2, and 19.8\%.\textsuperscript{26}

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(32) Hydrazoic acid was generated by the procedure reported in: Wolff, H. Org. React. 1946, 3, 327.
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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

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

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<th>solvent</th>
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$^a$24a (0.1–0.2 M), β-ketoester [R = Me (2 equiv); R = allyl (5 equiv)], Na$_2$SO$_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.

### Hydrogenation Studies and Double-Pulsed Field Gradient Spin–Echo NOE Studies of the Decahydro-5,6,8b-triazacenaphthalene Products

Since batzelladine alkaloids A (1), D (4), F (6), and G contain 4-methyl-7-allyl-1,2,2a,3,4,5,6,7,8,8a-decahydro-5,6,8b-triazacenaphthalene-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.$^{38}$

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-triazacenaphthalene-3-carboxylic acid 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.

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(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.$^{38}$ 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.


(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$_2$O$_3$, Ru/C, Ru/Al$_2$O$_3$, 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.$^{40}$
The stereochernistry 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 Methanalysis 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 Na2SO4 in CF3CH2OH 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 1H and 13C NMR, IR, and HRMS consistent with those reported for this degradation product of batzelladine B.2,44

**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 methanalysis 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 25R,28S,30R. The 4-methyl-7-alkyl-1,2,3a,4,5,6,7,8-tetrahydro-5,6,8b-triazazaacenaphthalene-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 be realized before practical access to this latter tricyclic fragment of the batzelladine alkaloids is achieved.44

**Experimental Section**

Methyl 3-Oxodecanoate (14b).13 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 Et2O (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 Et2O (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 Et2O–MeOH (4:1, 500 mL) and 1 M HCl (500 mL). The layers were separated, and the aqueous phase was extracted with Et2O (3 × 500 mL). The organic layers were combined, washed with saturated aqueous NaHCO3 (500 mL), dried (MgSO4), and concentrated to a dark yellow oil. The residue was purified by distillation under reduced pressure (bp 90 °C, 1 mm). Additional Et2O (300 mL) was added dropwise to the reaction mixture, and, when solidification was observed, azeotropic distillation under reduced pressure (bp 90 °C, 1 mm) was conducted. The purifying distillation produced 14b (30.1 g, 46%) as a colorless oil that solidified below 10 °C: 1H NMR (CDCl3, 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, 0.2H), 1.46 (t, J = 6.7 Hz, 2H), 1.16 (broad s, 8H), 0.75 (t, J = 6.6 Hz, 3H); 13C NMR (CDCl3, 75 MHz) 202.5, 178.5, 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 (Cl) m/z 201.1495 (201.1490 calcd for C11H21O3, MH)+, 159, 158, 127.

Methyl (3S)-Hydroxydecanoate (15b).15 (S)-BINALP–RuCl3 (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 N2.21 The vessel was evacuated and refilled with N2 (3 × 500 mL). The reaction was allowed to cool to room temperature and then heated to 40 °C with vigorous stirring for 6 h. The reaction was allowed to cool to room temperature and concentrated to 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: 1H NMR (CDCl3, 300 MHz) δ 3.96 (broad m, 1H), 3.67 (s, 3H), 2.91 (broad s, 1H), 2.28 (dd, J = 16.3, 3.4 Hz, 1H), 2.47 (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); 13C NMR (CDCl3, 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 (Cl) m/z 203.1650 (203.1647 calcd for C11H22O3, MH)+, 203, 185, 171, 153; [α]D25 +16.4, [α]D25 = 18.3, [α]D25 = +20.0, [α]D25 = +35.1, [α]D25 = +40.2 (c 1.0, CHCl3). Anal. Calcd for C11H22O3: C, 65.31; H, 10.96. Found: C, 65.18; H, 10.87.

(44) An improved route to the 2a,8a-anti series employing an alternate tethered Biginelli construction of the 4,7-disubstituted-1.2a,5,6,7,8-octahydro-5,6,8b-triazazaacenaphthalene-3-carboxylic acid subunit 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.

(35)-Hydroxy-N-methoxy-N-methyldecanamide (16b).
Following the general conditions of Weinreb,23 Me3Al (56 mL of a 2.0 M solution in toluene, 0.11 mol) was added dropwise to a suspension of N,N-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. A solution of the ester 15b (4.52 g, 0.03 mol) in toluene (90 mL) was added, and the reaction was allowed to warm to room temperature over 1 h and then quenched with aqueous 2 M tartaric acid (750 mL). The resulting biphasic mixture was stirred vigorously for 1.5 h, and the layers were separated. The aqueous phase was extracted with CH2Cl2 (3 × 300 mL), and the combined organic extracts were dried (MgSO4) and concentrated to give a yellow oil. This crude oil was purified by flash column chromatography (3:2 hexanes-2-propanol, 2.2 g, 40% yield) to give 4.33 g (94%) of diazide 19b as a pale yellow oil which solidified below 10 °C;

1H NMR (CDCl3, 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); 13C NMR (CDCl3, 75 MHz) 173.6, 67.3, 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 (Cl) m/z 232.1913 (232.1912 calcd for C12H26NO3, MH+); [α]25D + 98.8 (c 1.0, CHCl3). Anal. Calc. for C12H26NO3: C, 70.98; H, 10.89; N, 6.05. Found: C, 70.02; H, 10.84; N, 5.89.

(4S,6R,1,1-Dimethoxy-4,6-diazide (21b). LiAlH4 (29 mL of 1.0 M solution in THF, 29 mmol) was added dropwise to a solution of diazide 20b (3.1 g, 9.5 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, and the crude mixture was filtered, washed with 5% HCl (20 mL), and water (20 mL) at room temperature. After 3 h, the reaction mixture was concentrated to 0.5 M NaF (4.8 g, 114 mmol), H2O (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 further purification;

1H NMR (CDCl3, 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, 4H), 1.57–1.22 (m, 8H), 1.07–0.84 (m, 10H); 13C NMR (CDCl3, 75 MHz) 124.9, 37.6, 35.4, 32.1, 29.4, 29.0, 28.6, 26.5, 22.3, 13.8 ppm; IR (film) 3366, 3286 cm−1; MS (Cl) m/z 275.2695 (275.2698 calcd for C12H22N2O2, MH+), 285, 275, 253, 242, 181, 167, 154, 128; [α]20D −0.2, [α]20D + 1.1, [α]20D + 0.35, [α]20D + 1.8; [α]20D + 1.8, [α]20D + 12.0, [α]20D + 14.3 (c 1.0, CHCl3).

(4S,6R,2(2,2,2-Trichloroethoxy)carbonyl)l-4-(3,3-dimethyl-propoxypyramidine (23b). Following the general procedures of Kay and co-workers,33 a solution of diamine 21b (2.2 g, 8.02 mmol), carbonodithioic acid (2.5 g, 8.88 mmol), and CHCl3 (100 mL) was maintained at room temperature for 19 h. The reaction was concentrated, and the residue was purified by flash column chromatography (10:1 hexanes–EtOAc–Et2N) to give 3.10 g (82%) of guanidine 23b as a pale yellow oil that formed a white wax on standing at 0 °C;

1H NMR (CDCl3, 300 MHz) δ 4.03 (t, J = 7.7 Hz, 1H), 3.65–3.37 (broad m, 3H), 2.74–2.51 (m, 2H), 1.58–1.32 (m, 10H), 0.81 (t, J = 6.7 Hz, 3H); 13C NMR (CDCl3, 75 MHz) 104.5, 72.6, 60.2, 52.6, 42.6, 39.0, 32.7, 31.7, 25.5, 29.1, 28.4, 25.3, 22.5, 18.0 ppm; IR (film) 3420, 3260, 3062, 2934, 2928, 2854, 2828, 2770, 1738, 1528, 1510, 1465, 1443, 1420, 1375, 1284, 1262, 1214, 1184, 1152, 1134, 1080, 1059, 1020, 985, 937, 914, 889, 845, 772, 739, 717, 695, 674, 650, 628, 609, 594, 583, 569, 555, 539, 524, 511, 497, 483, 471, 457, 438, 420, 406 ppm; MS (Cl) m/z 275.2695 (275.2698 calcd for C12H22N2O2, MH+), 285, 275, 253, 242, 241, 194, 167, 154, 128; [α]23D −0.2, [α]23D + 1.1, [α]23D + 0.3, [α]23D + 1.8, [α]23D + 1.8, [α]23D −12.0, [α]23D −14.3 (c 1.0, CHCl3).

(3R,4aS)-1-Mino-7-hydroxy-3-heptyl-2,3,4,4aS,5,6,7,7a-tetrahydroxyprolyl-[1,2-c]-pyridinium Chloride (24b). Zinc dust (2.52 g, 38.5 mmol) was added to a solution of the protected guanidine 23b (1.0 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 H₂S. 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 concen-
trated. This light yellow residue was diluted in CH₂Cl₂ (50 mL) with HCl (1 N aqueous, 2.4 mL, 2.4 mmol) and was concen-
trated to give 620 mg (100%) of deprotected guanidine 15 as a 1:1 mixture of diastereoisomers. This light yellow oil was dissolved in the next step without further purification.

**H NMR (CDCl₃, 500 MHz)  δ 7.96 (aprop broad d, J = 36.9 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). 13C NMR (CDCl₃, 125 MHz) 152.9, 152.6, 82.6, 81.0, 80.3, 57.3, 55.0, 52.1, 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) 3218, 1694 cm⁻¹.

**Methyl (2R,7R,8aS)-7-Heptyl-4-methyl-1,2,2a,5,6,7,8a-octahydro-5,6,6b-triazaenanthenyl-3-carboxylate (10).** A solution of guanidine 24b (0.612 mg, 2.11 mmol), morpholine (0.18 mL, 2.33 mmol), glacial acetic acid (0.13 mL, 2.2 mmol), methyl acetate (0.45 mL, 4.4 mmol), Na₂SO₄ (492 mg, 3.46 mmol), and 1,1-dimethylethylamine (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 1:1 mixture of 25a and 26a as a colorless oil. This fraction was concentrated to give 21 mg (99%) of a 20:1 mixture of 25a and 26a as a colorless oil. This fraction was concentrated to give 21 mg (99%) of a 20:1 mixture of 25a and 26a as a yellow oil. These epimers were separated by preparative HPLC (5 μm Altimma reversed-phase C18 silica, 18x10.0 CIH₃CN–H₂O–TFA) to give isomeric pure tricyclic guanidine 25a (82 mg, 82%) and 7% (m) of the corresponding 26a epimer. Guanidine 25a [(α)²⁴D = +104, (α)³⁴D = -30.1, (α)²⁴S = -34.3, (α)³⁴S = -58.6, (α)²⁴C = -70.6 (c 1.0, CHCl₃)] showed 1H and 13C NMR in accord with reported data.³,⁹

**Bignelli 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, 2.33 mmol), Na₂SO₄ (492 mg, 3.46 mmol), and 1,1-dimethylethylamine (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 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 Altimma silica, 97:3.5:0.5 CH₃CN–MeOH–AcOH) to give pure samples of both isomers. 25a: [α]²⁴D = -41.9, [α]³⁴D = -11.9, [α]²⁴S = -221, [α]³⁴S = -277 (c 0.93, CH₃OH), showed 1H and 13C NMR in accord with reported data.³,⁹

**Hydrogenation of 25a with Pd/C in Methanol. Preparation of Methyl (2S,3S,4R,7aR,8aS)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8a-decahydro-5,6,6b-triazaenanthenyl 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 H₂ 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 isomeric pure 30.

**Hydrogenation of 25a with RhAl₂O₅ in Methanol.** Preparation of Methyl (2S,3S,4R,7aR,8aS)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8a-decahydro-5,6,6b-triazaenanthenyl 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 H₂ in the presence of RhAl₂O₅ (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: [α]²⁴H = 17.6, [α]³⁴H = 24.7 ([α]²⁴D = -40.8, [α]³⁴D = -52.1 (c 1.0, CH₃OH), showed 1H and 13C NMR in accord with reported data.³,⁹

**Hydrogenation of 25a with RhAl₂O₅ in Methanol.** Preparation of Methyl (2S,3S,4R,7aR,8aS)-4-Methyl-7-nonyl-1,2,2a,3,4,5,6,7,8a-decahydro-5,6,6b-triazaenanthenyl chloride-3-carboxylate (29). 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 H₂ in the presence of RhAl₂O₅ (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 29 and 30 as a colorless oil. This mixture was purified by preparative HPLC (5 μm Altimma reversed-phase C18 silica, 20:10.1 CH₃CN–H₂O–TFA) to give 29 (99%) and 30 (1%) as 20:1 mixtures.
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); DPGSENOE enhancements observed between H-2a and H-2 (strong), H-2a and 4-CH3 (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-CH3 (strong), 4-CH3 and H-2a (strong), 4-CH3 and H-3 (medium), 4-CH3 and H-4 (strong), H-7 and H-8a (strong), H-8a and H-2a (strong), H-8a and H-7 (strong); 13C NMR (CD3OD, 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 C21H38N3O2, 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.