Revision of the Stereochemistry of Batzelladine F. Approaches to the Tricyclic Hydroxyguanidine Moiety of Batzelladines G, H, and I

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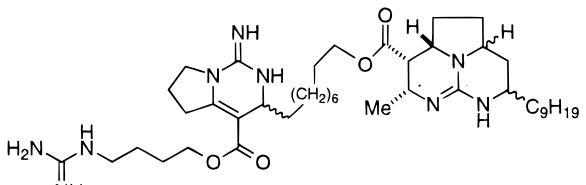
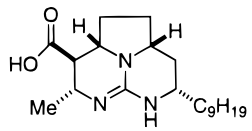
The polycyclic guanidine alkaloids batzelladines F−I isolated from a Jamaican sponge of the genus *Batzella* in 1997 are of potential value for the treatment of AIDS because they induce p56^{lck}-CD4 dissociation at micromolar concentrations. Comparison of the spectral data for both the synthetic syn and anti tricyclic left-hand portions of batzelladine F establishes that the natural product has the syn rather than the anti stereochemistry originally assigned. Approaches to the tricyclic hydroxyguanidine moiety of batzelladines G−I are described.

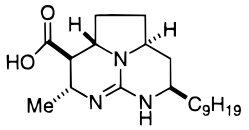
Patil and co-workers at SmithKline Beecham reported the isolation of the polycyclic guanidine batzelladines A−E from a Bahamian sponge of the genus *Batzella* in 1995.[1] Batzelladines A and B inhibit the binding of HIV-1 gp-120 to CD4 and are therefore of potential interest for the treatment of AIDS. The structures were elucidated by interpretation of spectral data and chemical degradation. Hydrolysis of batzelladine A (**1**) gave an acid assigned structure **3** resulting from epimerization of the axial carboxylate of **1**. We prepared both the syn acid **3** and the anti acid **4** by unambiguous methods and established by spectroscopic comparison that the hydrolysis product of batzelladine A had structure **4**, not **3**, and that the structure of batzelladine A must therefore be **2**, not **1**.[2,3,4] This assignment was confirmed by the SmithKline Beecham group by careful NOE studies on the hydrolysis product.[2]



1, β-H, α-C_9H_{19} (proposed structure of batzelladine A)
2, α-H, β-C_9H_{19} (corrected structure of batzelladine A)

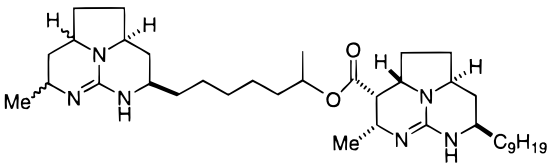


3 (proposed structure of hydrolysis product of batzelladine A)



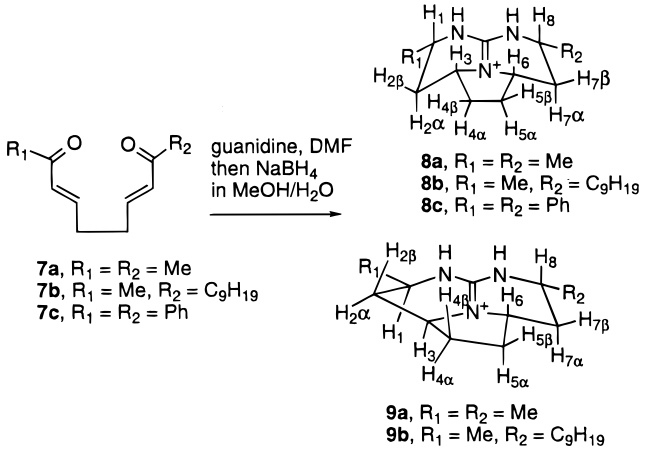
4 (corrected structure of hydrolysis product of batzelladine A)

Patil and co-workers reported the isolation of four additional polycyclic guanidines, batzelladines F−I, in 1997, from a Jamaican sponge of the genus *Batzella*.[5] These are also of potential value for the treatment of AIDS because they induce p56^{lck}-CD4 dissociation at micromolar concentrations. The right-hand portion of batzelladine F (**5**) is the same as that of batzelladine A. The left-hand portion was assigned anti stereochemistry based on NOE experiments analogous to those carried out on **4**. We were concerned by this assignment because the virtual symmetry of the two six-membered rings of the left-hand portion of batzelladine F suggested that these NOE experiments could not be carried out with a high degree of confidence.



5, β-H, α-Me (proposed structure of batzelladine F)
6, α-H, β-Me (corrected structure of batzelladine F)

In 1996, Murphy and co-workers reported the reaction of guanidine with the bis enones **7** to give intermediates that were reduced directly with sodium borohydride to give tricyclic guanidines **8** as a single stereoisomer.[6] The syn stereochemistry of **8c** was assigned by X-ray crystallography. The structure of the aliphatic analogues was assigned by analogy. Unfortunately, the NMR spectral data for **8** were reported in $CDCl_3$ so that they could not be compared to the spectral data for batzelladine F (**5**), which were reported in CD_3OD.



7a, $R_1 = R_2$ = Me
7b, R_1 = Me, $R_2 = C_9H_{19}$
7c, $R_1 = R_2$ = Ph

8a, $R_1 = R_2$ = Me
8b, R_1 = Me, $R_2 = C_9H_{19}$
8c, $R_1 = R_2$ = Ph

9a, $R_1 = R_2$ = Me
9b, R_1 = Me, $R_2 = C_9H_{19}$

We repeated the Murphy protocol and found that the ^1H and ^{13}C NMR spectral data for **8b** in CD_3OD were identical to those reported for the left-hand portion of batzelladine

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Table 1. Proton NMR Data for Syn and Anti Tricyclic Guanidines in CD_3OD[a]

atom	8a	9a	batzelladine F	8b	9b	3	4
Me	1.27[b]	1.27[b]	1.26[b]	1.26[b]	1.26[b]	1.26[b]	1.27[b]
1	3.55	3.63	3.52	3.54	3.62	3.55	3.62
2	2.23	2.28[d]	2.20	2.24	2.31[d]	1.87	1.99
2	1.26[c]	1.35[c]	1.25	1.23[c]	1.35	CO_2H	CO_2H
3	3.75	3.63	3.72	3.73	3.61	3.76	3.61
4	2.23	2.19	2.20	2.24	2.20	2.22	2.18
4	1.68	1.61	1.67	1.67	1.61	1.82	1.67
5	2.23	2.19	2.20	2.24	2.20	2.22	2.18
5	1.68	1.61	1.67	1.67	1.61	1.65	1.58
6	3.75	3.63	3.72	3.73	3.61	3.76	3.61
7	2.23	2.28[d]	2.28	2.26	2.31[d]	2.22	2.31
7	1.26[c]	1.35[c]	1.21	1.23[c]	1.35	1.23[c]	1.36
8	3.55	3.63	3.40	3.41	3.50	3.41	3.48

[a] All peaks are multiplets except where otherwise indicated. [b] d, J = 6.4 Hz. [c] ddd, J = 11, 11, 13 Hz. [d] ddd, J = 12.8, 4.5, 2.4 Hz.

Table 2. Carbon NMR Data for Syn and Anti Tricyclic Guanidines in CD_3OD

atom	8a	9a	batzelladine F	8b	9b	3	4
Me	20.8	21.7	20.7	20.7	21.7	19.3	20.3
1	47.2	48.0	47.2	47.3	48.8	50.5	52.1
2	36.8	36.4	36.9	36.8	36.5	56.2	55.0
3	57.4	56.5	57.5	57.5	56.5	60.5	59.2
4	31.0	31.8	31.1	31.1	31.8	29.9	30.3
5	31.0	31.8	31.1	31.1	31.8	31.2	31.7
6	57.4	56.5	57.4	57.5	56.4	58.1	56.7
7	36.8	36.4	34.8	34.8	34.3	34.9	34.2
8	47.2	48.0	51.6	51.6	53.1	51.7	53.2
R	20.8	21.7	35.8	35.9	36.9	36.0	36.9
C=N	150.9	151.0	151.2	151.2	151.2	150.8	151.0

F (see Tables 1 and 2). Murphy reached a similar conclusion in 1998[7] after this work was completed and suggested that the stereochemistry of the left-hand portion of batzelladine F was syn, not anti as claimed by Patil.

Revision of the Stereochemistry of the Left-Hand Tricycle of Batzelladine F. To establish definitively that the stereochemistry of the left-hand portion of batzelladine F is syn, not anti, we needed to establish both (a) that the data for the anti isomer should be significantly different from that of the syn isomer and (b) that the Murphy protocol affords syn tricyclic guanidines from aliphatic bis enones **7a** and **7b** as well as aromatic bis enone **7c**. We followed a slightly different procedure from Murphy and obtained 60% of a >10:1 mixture of **8a** and a minor product from the symmetrical bis enone **7a**. Careful chromatography afforded 9% of pure **8a** and 10% of a fraction that contained an 8−10:1 mixture of **8a** and a second compound. The ^1H and ^{13}C NMR spectral data of this minor product could be completely determined from the mixture by COSY, HSQC, and HMBC experiments (see Figures 1 and 2). A similar reaction with the unsymmetrical bis enone **7b** afforded 8% of pure **8b** and 9% of a 5:1 mixture of **8b** and a second component that could be characterized by the above 2D NMR experiments on the mixture.

The differences in the spectral data between these minor components and **8a** and **8b** correspond closely to those between the syn acid **3** and the anti acid **4** (see Tables 1 and 2), indicating that these minor compounds are the anti tricyclic guanidines **9a** and **9b**. Among the many significant differences, the methyl carbon absorbs 0.9−1.0 ppm upfield, C_3 and C_6 absorb 0.9−1.4 ppm downfield, C_1 and C_8 absorb 0.8−1.6 ppm upfield, H_1 and H_8 absorb 0.07−0.08 ppm upfield, $H_{2\alpha}$ and $H_{7\alpha}$ absorb 0.09−0.13 ppm upfield, and H_3 and H_6 absorb 0.12−0.15 ppm downfield in the syn isomers **3**, **8a**, and **8b**.

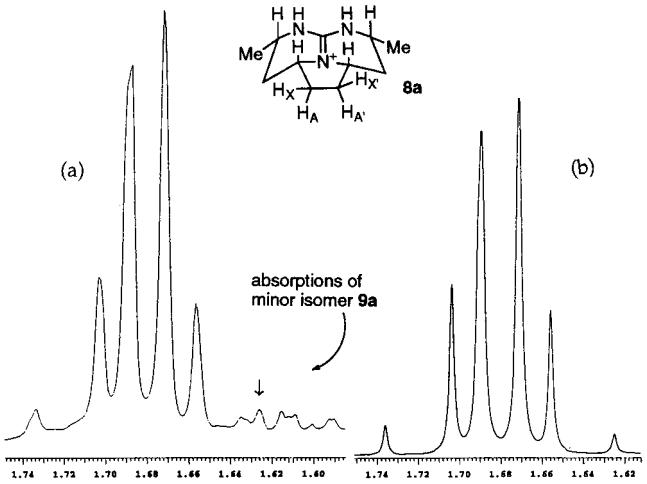


Figure 1. (a) Observed spectrum for the upfield pyrrolidine methylene hydrogens of **8a** at δ 1.62−1.74 (H_A, $H_{A'}$) with decoupling of the ring fusion hydrogens at δ 3.75. (b) Calculated spectrum for H_A and $H_{A'}$ of an AA′XX′ pattern with $J_{AA'}$ = 9 Hz, $J_{X,X'}$ = 9 Hz, $J_{AX'}$ = $J_{A'X}$ = 6 Hz, and J_{AX} = $J_{A'X'}$ = −13 Hz.

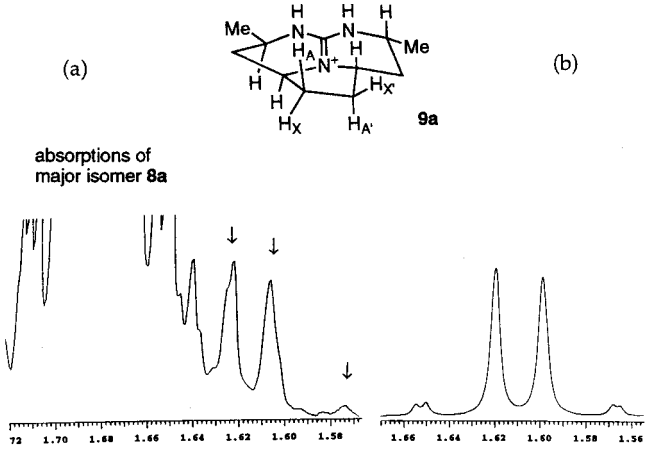


Figure 2. (a) Observed spectrum for the upfield pyrrolidine methylene hydrogens of **9a** at δ 1.59−1.64 (H_A, $H_{A'}$) with decoupling of the ring fusion hydrogens at δ 3.63. (b) Calculated spectrum for H_A and $H_{A'}$ of an AA′XX′ pattern with $J_{AA'}$ = 13 Hz, $J_{X,X'}$ = 1 Hz, $J_{AX'}$ = $J_{A'X}$ = 5 Hz, and J_{AX} = $J_{A'X'}$ = −13 Hz.

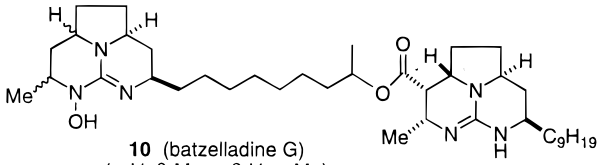
We have thus established that the data for the anti isomers **4**, **9a**, and **9b** are significantly different from those of the syn isomers. However, the assignment of the syn stereochemistry of the major products rests on the crystal structure of **8c** and the comparison of the spectral data of **8** and **9** to those of the acids **3** and **4**, which were prepared by unambiguous routes and characterized by NOE. We therefore confirmed the stereochemical assignment of **8** and **9** by analysis of the coupling constants in the proton NMR spectra.

Decoupling H_3 and H_6 should collapse the methylene groups on the five-membered ring to AA′XX′ multiplets. MM2 calculations indicated that the syn isomer **8a** should exist in three conformers with Boltzmann averaged coupling constants of $H_{4\alpha,5\alpha}$ = 9 Hz, $H_{4\alpha,5\beta}$ = $H_{4\beta,5\alpha}$ = 6 Hz, and $H_{4\beta,5\beta}$ = 9 Hz.[8] Using a value of −13 Hz for the geminal coupling constants, we calculated the pattern for $H_{4\alpha}$ and $H_{5\alpha}$ at δ 1.62−1.74 shown in Figure 1. Decoupling H_3 and H_6 of the major product at δ 3.75 produces a pattern at δ 1.62−1.74 (see Figure 1) corresponding very closely to that calculated for the syn isomer. The anti isomer **9a** can only exist in one conformer with calculated coupling constants of $H_{4\beta,5\alpha}$ = 13 Hz, $H_{4\alpha,5\alpha}$ = $H_{4\beta,5\beta}$ = 5 Hz, and $H_{4\alpha,5\beta}$ = 1 Hz.[8] Using a value of −13 Hz for the geminal coupling

constants we calculated the pattern for $H_{4\beta}$ and $H_{5\alpha}$ at δ 1.59−1.64 shown in Figure 2. Similarly, decoupling H_3 and H_6 of the minor product at δ 3.63 produces a pattern at δ 1.59−1.64 (see Figure 2) that corresponds well with calculated for the anti isomer, although the analysis is complicated by peaks for the major isomer. These results unambiguously confirm that the major product is the syn isomer **8a** and the minor product is the anti isomer **9a**. A similar experiment established that the major product from **7b** is the syn isomer **8b**.

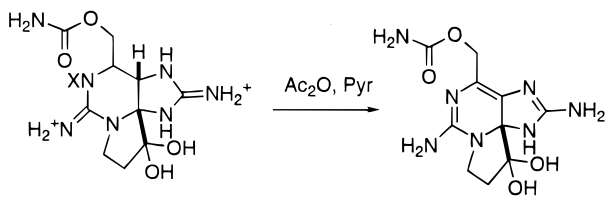
We have now unambiguously assigned syn stereochemistry to the major adducts **8a** and **8b** and shown that the minor anti adducts **9a** and **9b** have different NMR spectra. Because batzelladine F has spectra similar to those of the major isomer, its structure must be revised from **5** to **6**, with the left-hand ring system syn fused and the right-hand ring system anti fused.

Approaches to the Tricyclic Hydroxyguanidine of Batzelladines G−I. Batzelladine G (**10**) is identical to batzelladine F except for the presence of a hydroxy group on the guanidine nitrogen adjacent to the methyl group in the left-hand tricycle and two additional methylene groups in the chain connecting the two ring systems. The syn/anti stereochemistry of the left-hand tricycle is not known. The original anti assignment can no longer be accepted in view of the revision of the stereochemistry of batzelladine F to syn. Batzelladine H contains the identical left-hand tricyclic ring system as batzelladine G, while batzelladine I contains the same ring system with the hydroxy group on the other nitrogen.



10 (batzelladine G)
(α-H, β-Me or β-H, α-Me)

Cyclic hydroxyguanidines have previously been observed in the well-studied saxitoxin family.[9] Neosaxitoxin (**11**) was isolated as the major toxin in the cultured dinoflagellate, *Gonyaulax tamernsis*. However, the major toxin in the soft-shell clam *Mya arenaria* infested by the dinoflagellate is saxitoxin (**12**), suggesting that the shellfish reduces neosaxitoxin to saxitoxin.[9] This reduction can be carried out in the laboratory with Zn in acetic acid or sodium borohydride. Neosaxitoxin also dehydrates under mild conditions. Treatment of **11** with Ac_2O in pyridine at 25 °C afforded a compound tentatively characterized as the dehydration product **13**.[9] These results suggest that batzelladine F (**6**) may be biosynthesized by reduction of a hydroxyguanidine analogous to batzelladine G (**10**), and that the hydroxyguanidine moiety of batzelladine G should be easily dehydrated. Nevertheless, we decided to investigate oxidation of **8** as a route to the tricyclic hydroxyguanidine moieties of batzelladines G−I.



11, X = OH (neosaxitoxin)
12, X = H (saxitoxin)

13

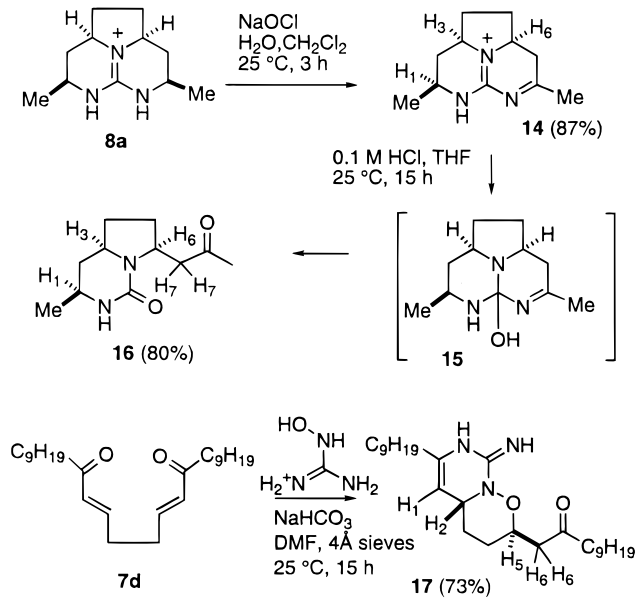
Oxidation of **8a** or **8b** with a variety of oxidants either gave no reaction or a complex mixture of products. Fortunately, oxidation of **8a** with aqueous NaOCl in CH_2Cl_2 proceeded cleanly, giving 87% of the unstable dehydro product **14**. The methyl groups absorb at δ 2.21 and 1.20 (d, J = 6 Hz). The methylene protons in the right-hand ring are shifted downfield to δ 3.25 (dd, J = 13.8, 3.1 Hz) and 2.35 (dd, J = 13.8, 9.0 Hz). The IR spectrum shows absorptions at 1650 and 1605 cm^{-1}, but no carbonyl peak. These data are analogous to those of known 4,5-dihydropyrimidines.[10] Presumably oxidation of **8a** affords the *N*-chloro compound, which undergoes facile elimination, as in the formation of **13**, to give **14**. The imine of **14** is relatively stable, possibly because the guanidinium ion retards acid-catalyzed hydrolysis of the imine, but decomposes on standing in CD_3OD.

Treatment of **14** with 0.1 M HCl in THF for 15 h at 25 °C hydrolyzes both the guanidine and the imine, affording 80% of the stable keto urea **16**, which could be fully characterized. The methyl groups absorb at δ 2.14 and 1.19 (d, J = 6.1 Hz). The methylene protons adjacent to the ketone (H_7) absorb at δ 3.45 (dd, J = 16.8, 3.1 Hz) and 2.28 (dd, J = 16.8, 9.8 Hz). The geminal coupling constant increases from 13.8 Hz in **14** to 16.8 Hz in **16** as expected for a methylene group adjacent to a ketone. The IR spectrum shows a carbonyl absorption at 1710 cm^{-1}. The presence of the urea, rather than the expected guanidinium cation was established by HRMS. Although the guanidinium group of arginine is stable in 6 N HCl at 110 °C for extended periods,[11] the guanidinium group of **14** hydrolyzes in dilute HCl at room temperature. The nitrogen of the imine double bond is not involved in resonance, so that the guanidine of **14** should behave more like an amidine, which should undergo attack by water to give **15**, which will then react further to give keto urea **16**. These results indicate that **8a** can be oxidized cleanly, but that the oxidation product eliminates readily, suggesting that it will be very difficult to oxidize **8** under mild enough conditions to permit the isolation of the hydroxyguanidine.

We therefore turned our attention to the reaction of hydroxyguanidine with **7**. Reaction of **7d** with hydroxyguanidinium sulfate[12] and $NaHCO_3$ in DMF for 15 h at 25 °C afforded 73% of **17**.[13] H_1 absorbs at δ 4.57 (d, J = 4.2 Hz) and H_2 and H_5 absorb as a two-proton multiplet at δ 4.28−4.38. The methylene protons adjacent to the carbonyl group (H_6) absorb at δ 2.72 (dd, J = 18.9, 9.8) and 2.61 (dd, 1, J = 18.9, 2.4). A 1D NOESY experiment with irradiation of these methylene protons produced a peak for H_5 at δ 4.33 (br dd, J = 10, 12). The 12 Hz coupling constant between H_5 and the adjacent axial ring hydrogen indicates that H_5 is axial. A 1D NOESY experiment with irradiation of H_1 at δ 4.57 produced a peak for H_2 at δ 4.33 (br d, J = 11). The 11 Hz coupling constant between H_2 and the adjacent ring hydrogen indicates that H_2 is also axial, and, therefore, that H_2 and H_5 are trans to each other.

The most likely mechanism for the formation of **17** involves the conjugate addition of the hydroxy-substituted guanidine nitrogen to the enone followed by enamine formation and conjugate addition of the hydroxy group to the other enone in undetermined order. The formation of the left-hand ring system of batzelladines G−H would have occurred if the unsubstituted guanidine nitrogens undergo conjugated addition preferentially. Apparently, the hydroxy group makes the nitrogen a better nucleophile for conjugate addition, as has been observed in an intramolecular S_N2

reaction of a benzyloxyguanidine[14] and intermolecular S_N2 reactions of methoxyguanidine.[15]



In conclusion, we have unambiguously established that the left-hand tricyclic ring system of batzelladine F (**6**) has the syn rather than anti stereochemistry originally assigned. Our approaches to the hydroxyguanidine moiety of batzelladines G−I have shed further light on the oxidation chemistry of guanidines and the use of hydroxyguanidine as a nucleophile for conjugate addition.

Experimental Section

Preparation of Starting Materials. Butanedial was prepared by hydrolysis of 2,5-dimethoxytetrahydrofuran[16] and converted to bis enones **7a**, **7b**, and **7d** by the procedure of Murphy.[6,7] Guanidine was prepared from guanidinium carbonate (460 mg, 2.56 mmol) by sonication with NaOMe in dry methanol under nitrogen.[17]

Reaction of (3*E*,7*E*)-Deca-3,7-diene-2,9-dione (7a) with Guanidine. A solution of freshly prepared free guanidine (354 mg, 6 mmol) in 3 mL of DMF was added dropwise to a solution of **7a** (500 mg, 3 mmol) in DMF (3 mL) at 0 °C. The reaction mixture was warmed to 25 °C over 1 h and stirred for 5 h. The reaction mixture was cooled to 0 °C and 3:1 MeOH−H_2O (8 mL) and $NaBH_4$ (227 mg, 6 mmol) were added. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was cooled to 0 °C, carefully treated with 1 N HCl (6 mL), and stirred for 30 min. The reaction mixture was allowed to warm to 25 °C, and saturated aqueous $NaBF_4$ solution was added. The reaction mixture was stirred for 45 min and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **8a** and **9a**, which were separated from the polymer by flash chromatography on Si gel (10:1 CH_2Cl_2−MeOH) to give 523 mg (60%) of a >10:1 mixture of **8a** and **9a** as determined by analysis of the ^1H and ^{13}C NMR spectra. Careful flash chromatography on Si gel twice, (first, 15:1:0.001 CH_2Cl_2−MeOH−HCOOH; second, 30:1:0.001 CH_2Cl_2−MeOH−HCOOH) gave 85 mg (10%) of an 8−10:1 mixture of (2aα,4*β*,7*β*,8aα)-2,2a,3,4,5,7,8,-8a-octahydro-4,7-dimethyl-1*H*-5,6,8b-triazaacenaphthylene tetrafluoroborate (**8a**) and (2aα,4*β*,7α,8a*β*)-2,2a,3,4,5,7,8,8a-octahydro-4,7-dimethyl-1*H*-5,6,8b-triazaacenaphthylene tetrafluoroborate (**9a**), followed by 77 mg (9%) of pure **8a**. Spectral data are shown in Tables 1 and 2.

Reaction of (3*E*,7*E*)-Octadeca-3,7-diene-2,9-dione (7b) with Guanidine. Free guanidine (289 mg, 4.05 mmol) and **7b** (663 mg, 2.4 mmol) were converted to 570 mg (62%) of crude **8b** and **9b** as described for **7a** above. The ^1H and ^{13}C NMR spectra of the crude product showed the presence of two isomers in approximately 10:1 ratio. Purification of 300 mg of the mixture by flash chromatography on Si gel twice (first, 20:1:0.001 CH_2Cl_2−MeOH−CHOOH and second, 30:1:0.001 CH_2Cl_2−MeOH−HCOOH) gave 44 mg (9%) of a 5:1 mixture of (2aα,4*β*,7*β*,8aα)-2,2a,3,4,5,7,8,8a-octahydro-4-methyl-7-nonyl-1*H*-5,6,8b-triazaacenaphthylene tetrafluoroborate (**8b**) and (2aα,4*β*,7α,8a*β*)-2,2a,3,4,5,7,8,8a-octahydro-4-methyl-7-nonyl-1*H*-5,6,8b-triazaacenaph-thylene tetrafluoroborate (**9b**), followed by 36 mg (8%) of **8b**. Spectral data are shown in Tables 1 and 2.

(2aα,4*β*,8aα)-2,2a,3,4,8,8a-Hexahydro-4,7-dimethyl-1*H*-5,6,8b-triazaacenaphthylene Tetrafluoroborate (14). Sodium hypochlorite solution (5.25% in H_2O, Chlorox, 2 mL) was added to a solution of **8a** (30 mg, 0.1 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 3 h. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 26 mg (87%) of **14**: ^1H NMR ($CDCl_3$) 4.36 (br s, NH), 4.19 (br ddd, 1, J = 3, 9, 7 Hz, H_6), 3.53 (m, 2, H_1 and H_3), 3.25 (dd, 1, J = 3.1, 13.8 Hz, $H_{7\alpha}$), 2.35 (dd, 1, J = 9, 13.8 Hz, $H_{7\beta}$), 2.21 (s, 3), 2.11 (br d, 1, J = 12.8 Hz, $H_{2\alpha}$), 2.00 (ddd, 1, J = 5.5, 6.1, 11.6 Hz, $H_{5\alpha}$), 1.85−1.80 (m, 2, H_4), 1.55 (dddd, 1, J = 6.7, 12, 12, 12 Hz, $H_{5\beta}$), 1.21−1.15 (m, 1, $H_{2\beta}$), 1.20 (d, 3, J = 6 Hz); ^{13}C NMR ($CDCl_3$) 180.1, 154.8, 57.0, 53.5, 47.5, 44.0, 37.0, 30.3, 28.0, 22.3, 22.1; IR (CH_2Cl_2) 3434, 1650, 1605.

(3α,4a*β*,7α)-Hexahydro-3-methyl-7-(2-oxopropyl)-pyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one (16). Oxidation product **14** (20 mg, 0.09 mmol) was dissolved in THF (3 mL) containing 0.5 mL of 0.1 N HCl. The reaction mixture was stirred for 15 h at 25 °C. The solvent was evaporated under reduced pressure giving 20 mg of crude product that was purified on Si gel (20:1 CH_2Cl_2−MeOH) to yield 16 mg (80%) of **16**: ^1H NMR ($CDCl_3$) 4.34 (br s, 1, NH), 4.28 (br ddd, 1, J = 3, 9, 10 Hz, H_6), 3.50−3.45 (m, 2, H_1 and H_3), 3.45 (dd, 1, J = 3.1, 16.8 Hz, H_7), 2.28 (dd, 1, J = 9.8, 16.8 Hz, H_7), 2.14 (s, 3), 2.10 (br d, 1, J = 12.8 Hz, $H_{2\alpha}$), 2.06−1.94 (m, 2, $H_{4\alpha}$ and $H_{5\alpha}$), 1.72 (dd, 1, J = 6.7, 12.2 Hz, $H_{5\alpha}$), 1.50−1.45 (m, 1, $H_{4\alpha}$), 1.19 (d, 3, J = 6.1 Hz), 1.18 (ddd, 1, J = 12, 12, 12 Hz, $H_{2\beta}$); ^{13}C NMR ($CDCl_3$) 207.7, 155.0, 56.9, 52.6, 47.6, 47.3, 37.2, 30.4, 30.3, 29.2, 22.3; IR (CH_2Cl_2) 3435, 1710, 1649, 1602; EIMS *m*/*z* 210 (M^+, 6), 168 (14), 167 (60), 153 (35), 136 (9), 121 (21), 119 (34); HREIMS calcd for $C_{11}H_{18}N_2O_3$ 210.1368; found 210.1373.

(2*β*,4a*β*)-1-{2-(8-Amino-2,3,4,4a-tetrahydro-6-nonylpyrimido[3,4-*b*][1,2]oxazinyl)}-2-undecanone (17). A solution of **7d** (240 mg, 0.6 mmol), *N*-hydroxyguanidinium sulfate[12] (346 mg, 1.3 mmol), and $NaHCO_3$ (218 mg, 2.6 mmol) in 5 mL of DMF containing 4 Å molecular sieves (10−15 pellets) was stirred under nitrogen at 25 °C for 15 h. The reaction mixture was treated with brine (10 mL) and extracted with 3:1 EtOAc−CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a thick oil that was treated with hexane to give 200 mg (73%) of **17** as a yellowish solid: mp 88−90 °C; ^1H NMR ($CDCl_3$) 4.57 (d, 1, J = 4.2 Hz, H_1), 4.38−4.28 (m, 2, H_2 and H_5), 2.72 (dd, 1, J = 9.8, 18.9 Hz, H_6), 2.61 (dd, 1, J = 2.4, 18.9 Hz, H_6), 2.42 (t, 2, J = 7.9 Hz), 2.10 (br t, 2, J = 7.6 Hz) 1.87−1.65 (m, 4, H_3 and H_4), 1.60−1.50 (m, 4), 1.40−1.20 (br s, 24), 0.88 (t, 3, J = 7.3 Hz), 0.87 (t, 3, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) 208.3, 151.6, 134.8, 98.1, 77.6, 55.3, 45.4, 42.9, 31.86, 31.79, 31.77, 30.7, 29.5, 29.31, 29.28, 29.2, 29.18, 29.16, 29.0, 28.9, 28.7, 26.2, 23.5, 22.6 (2 C), 14.0 (2 C); IR (CH_2Cl_2) 1712, 1668, 1607; HRFABMS calcd for $C_{27}H_{50}N_3O_2$ [MH^+] 448.3903; found 448.3902; decoupling at δ 4.33 (H_2 and H_5) collapsed the peak at δ 4.57 (H_1) to a singlet and the peaks at δ 2.72 and 2.61 to doublets (J = 18.9 Hz). A 1D NOESY experiment with irradiation of H_6 at δ 2.72−2.61 produced a peak at δ 4.33 (br dd, J = 10, 12 Hz, H_5). A 1D NOESY experiment with irradiation at δ 4.57 produced a peak at δ 4.33 (br d, J = 11 Hz, H_2).

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