# Biomimetic Syntheses of (±)-Crambines A, B, C1, and C2. Revision of the Structures of Crambines B and C1

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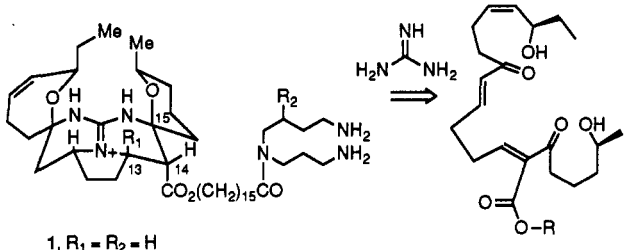
*Received March 9, 1993*

Crambines A (**7**) (eight steps, 22%), B (**45d**) (eight steps, 19%), C1 (**9d**) (seven steps, 21%), and C2 (**9a**) (seven steps, 27%) have been synthesized expediently and stereospecifically by a biomimetic route from methyl acetoacetate. Aminodihydropyrimidines **39** and **40** are formed efficiently from enone ester **36** by a two-step procedure involving addition of *O*-methylisourea to give methoxydihydropyrimidine **37** followed by displacement of the methoxy group of **37** with ammonia. Hydrogenolysis of **40a** and **40d** afford crambines C2 and C1, respectively. Mesylation of the alcohol of **39a** or **40a** followed by $Et_3N$-catalyzed cyclization and hydrogenolysis affords crambine A (**7**). Aminal formation from **39d** or **40d** in $CHCl_3$ followed by hydrogenolysis proceeds stereospecifically to provide crambine B (**45d**). The structure of crambine B has been revised to the stereochemistry shown in **45** and both crambines B and C1 have a seven rather than five-carbon guanidino alkyl chain.

## Introduction

Kashman and Kakisawa reported the isolation of the novel polycyclic guanidine alkaloid ptilomycalin A (**1**) from the Caribbean sponge *Ptilocaulis spiculifer* and from a red *Hemimycale sp.* of the Red Sea in 1989.[1] Ptilomycalin A shows cytotoxicity against P388 with $IC_{50}$ = 0.1 μg/mL and antifungal and antimicrobial activity against *Candida albicans* (MIC = 0.8 μg/mL) as well as antiviral activity (HSV) at 0.2 μg/mL. The structure was determined by a combination of 1D and 2D NMR experiments. Rinehart reported the isolation of the closely related antiviral and cytotoxic crambescidins from the red, encrusting Mediterranean sponge *Crambe crambe* in 1991.[2] The crambescidins have the same pentacyclic guanidine moiety with an additional hydroxy group on the side chain in crambescidin 800 (**3**) and on both the ring and side chain in crambescidin 816 (**2**).




1, $R_1 = R_2 = H$
2, $R_1 = R_2 = OH$
3, $R_1 = H$, $R_2 = OH$

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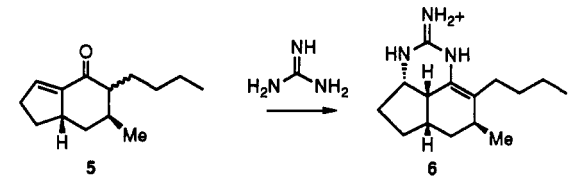
We were intrigued by the structural similarities between ptilomycalin A (**1**) and ptilocaulin (**6**), which was isolated earlier from *Ptilocaulis spiculifer* by Rinehart.[3] We reported the first synthesis of ptilocaulin in 1983, which was based on the retrosynthetic analysis that ptilocaulin could be prepared by Michael addition of guanidine to enone **5** followed by intramolecular enamine formation.[4]

The facile formation of ptilocaulin (**6**) from **5** and guanidine suggests that the biosynthesis of ptilocaulin, and perhaps

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**1** as well, involves the addition of guanidine to a polyketide in the last step. This analysis suggests that addition of guanidine to the double Michael acceptor **4** followed by imine and then aminal formation could give the pentacyclic framework of **1** in a single step.

Braekman and co-workers reported the isolation of the icthyotoxic guanidine alkaloids crambines A (**7**) and B (**8**) from *Crambe crambe* in 1990.[5] In 1992, they reported the isolation of two additional icthyotoxic compounds, crambine C1 (**9b**) and C2 (**9a**).[6] We chose to carry out syntheses of these alkaloids as a model study for the synthesis of ptilomycalin A (**1**). The spirocyclic framework of crambine B (**8**) is quite similar to the two right hand rings of **1**. The stereochemistry at C-7 and C-13 in crambine B is identical to that at C-13 and C-14 in ptilomycalin A. The stereochemistry of the aminal linkage (C-8 in **8** and C-15 in **1**) is different. However, the stereochemistry of this center of crambine B was tentatively assigned based only on the NOE between H-7 and H-9. If the stereochemistry of the aminal linkage in crambine B is the same as in ptilomycalin A, the methods developed in the synthesis of crambine B should prove applicable to the synthesis of the more complex target ptilomycalin A.

**Retrosynthetic Analysis.** Our retrosynthetic analysis suggested that crambine B (**8**) should be formed readily by acid- or base-catalyzed cyclization of crambine C1 (**9b**).[7] Similarly, crambine A (**7**) should be available by conversion

(1) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472.

(2) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712.

(3) Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L., Jr.; Shaw, P. D.; Hughes, R. G., Jr.; Mizsak, S. A.; Coats, J. H.; Zurenko, G. E.; Li, L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5604.

(4) Snider, B. B.; Faith, W. C. *Tetrahedron Lett.* **1983**, *24*, 861 and *J. Am. Chem. Soc.* **1984**, *106*, 1443.

(5) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Riccio, R. *Tetrahedron Lett.* **1990**, *31*, 6531.

(6) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, D.; Amade, P. *J. Nat. Prod.* **1992**, *55*, 528.

(7) For a preliminary report on a portion of this work see: Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526.

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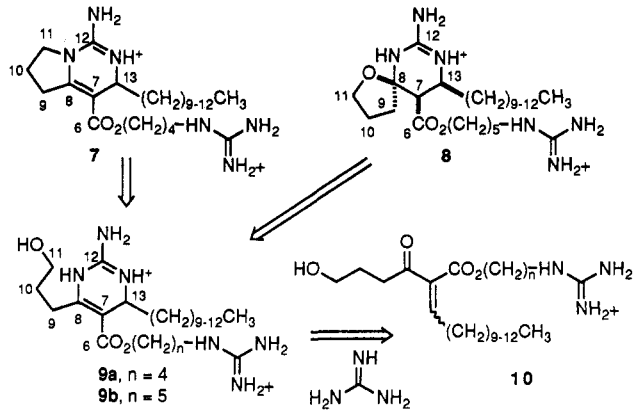
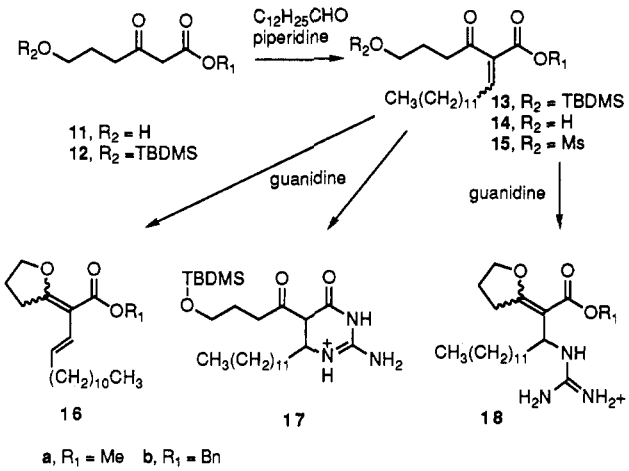



of the alcohol of crambine C2 (**9a**) to a leaving group followed by base-catalyzed cyclization. Crambines C1 and C2 (**9**) should be accessible by Michael addition of guanidine to enone ester **10** followed by enamine formation. Although the addition of guanidine to enones to form dihydropyrimidines has been extensively investigated,[8-10] the addition of guanidine or amidines to enone esters leads to the formation of tetrahydropyrimidinones (e.g. **17**) by Michael addition and amide formation in addition to, or instead of, the desired dihydropyrimidines.[11,12]

The presence of the guanidino alkyl side chain complicates the development of procedures for the synthesis of the monocyclic guanidine moiety of crambines C1 and C2 and the bicyclic guanidine moieties of crambines A and B. Therefore we chose to prepare the corresponding methyl esters in a model study and to postpone the problems of the guanidine-bearing side chain until procedures had been developed for the preparation of the cyclic moieties of the crambines.

## Results and Discussion

**Syntheses of Methyl Esters of the Cyclic Guanidine Moieties of Crambines A (23a), B (26a), and C (21a).** Alkylation of the dianion of methyl acetoacetate with ethylene oxide as previously reported affords **11a**, which cyclizes spontaneously to methyl tetrahydrofuranylideneacetate.[13] The hydroxy group of **11a** must be protected prior to workup. Reaction of 1 equiv of ethylene oxide with the dianion of methyl acetoacetate in THF (0 °C, 2 h) followed by addition of TBDMSCl (rt, 12 h) to the reaction mixture affords 58% of **12a**.[14] Knoevenagel condensation[15] of **12a** with tridecanal (benzene, catalytic piperidine 1 h at rt, 30 min at 80 °C and 12 h at rt) provides 88% of **13a** as a 1.1:1 mixture of *E*/*Z* isomers.[16] Unfortunately, addition of guanidine (prepared from the carbonate[17]) to **13a** in *tert*-butanol (5 h, rt) gives 71% of tetrahydropyrimidinone **17** as the only product. Similar results were obtained in several other solvents.




Mesylate **15a** was prepared as a potential precursor to crambine A (**7**). Hydrolysis of **13a** in 1:1:3 THF–$H_2O$–AcOH (6 h, rt) affords 90% of crude **14a** that cyclizes to give 64% of **16a** on chromatography. Reaction of crude **14a** with MsCl ($CH_2Cl_2$, $Et_3N$, 0 °C, 2 h) affords 84% of mesylate **15a**. Addition of guanidine[17] to mesylate **15a** in acetone (10 h, rt) affords 14% of **16a**, 40% of **18a** as a 1:1 mixture of *E*/*Z* isomers,[18] and 40% of material which appears to result from the addition of the guanidine of **18a** to a second molecule of **15a**.

**Syntheses of the Acyl Portions of Crambines B (26a) and C (21a).** These results demonstrate that guanidine cannot be added directly to **13a** or **15a** to give the desired dihydropyrimidine products. We therefore turned our attention to a two-step route involving the addition of less basic *O*-methylisourea to **13a** and conversion of methoxydihydropyrimidine **20a** to aminodihydropyrimidine **21a** that has been used successfully on other enone esters.[19] Reaction of **13a**, *O*-methylisourea sulfate (2 equiv), and $NaHCO_3$ (7 equiv) in DMF for 12 h at 60 °C furnishes 79% of the desired dihydropyrimidine **19a**. Hydrolysis of the silyl ether (TBAF, THF, 12 h, rt) yields 90% of the desired methoxydihydropyrimidine **20a** and 4% of the corresponding urea **28**.

The amino group was introduced by heating a solution of **20a** and $NH_4OAc$ (1.5 equiv) in MeOH saturated with anhydrous $NH_3$ at 60 °C for 2 d[19] providing 61% of **21a** and 37% of a 1:6:10 mixture of **24a** or **26a**, **25a**, and **26a** or **24a**, respectively. The $^1H$ and $^{13}C$ NMR spectra of aminodihydropyrimidine **21a** are identical to those reported for the acyl portion of crambines C1 and C2 (**9**).[6] The $^1H$ and $^{13}C$ NMR spectra of the major spiroaminal **24a** or **26a** are identical to those reported for the acyl portion of crambine B (**8**),[5] with the exception of slight shifts in the $^{13}C$ spectra due to the different ester, while the spectral data of the other two spiro aminals and are quite different.[20]

**Revision of the Stereochemistry of Crambine B.** The similarity of NMR data demonstrates that the major spiro aminal has the same stereochemistry as crambine B.

(8) Wendelin, W.; Schermanz, K.; *J. Heterocycl. Chem.* **1984**, *21*, 65 and refs cited therein.
(9) Weis, A. *Synthesis* **1985**, 528.
(10) Kim, Y. H.; Yoon, C. M.; Lee, N. J. *Heterocycles* **1981**, *16*, 49.
(11) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. *J. Org. Chem.* **1985**, *50*, 4227.
(12) Weis, A. L.; Vishkautsan, R. *Isr. J. Chem.* **1986**, *27*, 105.
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(14) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.
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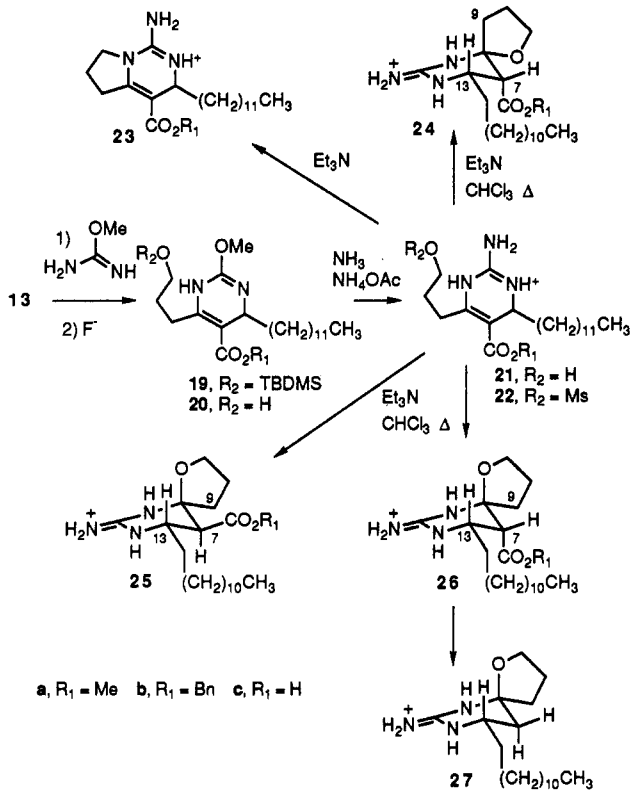
(16) Bogdanov, V. S.; Ugrak, B. I.; Krasnaya, Zh. A.; Stytsenko, T. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 356. *Bull. Acad. Sci. USSR, Chem. Ser.* **1990**, 298.
(17) Uyehara, T.; Furuta, T.; Kabawawa, Y.; Yamada, J.-I.; Kato, T.; Yamamoto, Y. *J. Org. Chem.* **1988**, *53*, 3669.
(18) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550.
(19) (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185 and 1189. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
(20) We thank Prof. Braekman for spectral data of crambines A and B and for an authentic sample of crambine B.




However, the stereochemistry at the aminal center C-8 must still be assigned. The relative stereochemistry at C-7 and C-13 is easily established by the coupling constant between H-7 and H-13 which is 4.0-4.2 Hz in the cis isomers **24a** and **26a** and 11.5 Hz in the trans isomer **25a**. The stereochemistry of the aminal center must be determined by NOE experiments. ROESY experiments were reported to show an NOE between H-7 and H-9 in crambine B.[5] This does not mean that H-7 is cis to C-9 since examination of models suggests that the dihedral angle between H-7 and C-9 is 60° in both **24a** and **26a**. As expected, the ROESY spectra shows intense cross peaks between H-7 and H-9 and between H-7 and H-13 in both **24a** and **26a**.[21]

An NOE between H-9 and H-13 would conclusively establish the stereochemistry of the aminal center since this distance is calculated to be 2.5–3.0 Å in **24a** and 4.5–5.0 Å in **26a**. The ROESY spectra shows intense cross peaks between H-9 and H-13 in the minor spiro aminal and no cross peak in the major spiro aminal. *Therefore the major isomer is **26a**, not **24a**.* This stereochemistry assignment is supported by the chemical shift of H-13, which absorbs downfield by 0.16 ppm in the major isomer **26a** since it is deshielded by the axial oxygen.[22] Since the spectral data indicate that the major spiro aminal **26a** has the same stereochemistry as the natural product, *crambine B has the opposite stereochemistry at C-8 to that shown in 8* and therefore the same stereochemistry as at C-15 of ptilomycalin A.

The stereochemistry of the aminal center in **25a** was also established by 2D NMR. The ROESY spectrum shows an intense cross peak between H-7 and H-9. H-7 must be axial since the coupling constant between H-7 and H-13 is 11.5 Hz. Therefore, C-9 must be equatorial since H-9 is close to H-7. This establishes that the oxygen in **25a** is axial, as in the major isomer **26a**. The stereochemical assignment is confirmed by the absence of a cross peak between H-9 and H-13.

**Stereoselective Cyclization of 21a to the Cyclic Moiety of Crambine B (26a).** The 61:22:13:2 mixture of **21a** and spiro aminals **26a**, **25a**, and **24a**, respectively, appears to be an equilibrium mixture that can be established in methanol under either acidic or basic conditions. Heating either **21a** or the mixture of aminals for 1 d at 60 °C in methanol containing $Et_3N$ or for 3 d at 60 °C in methanol containing HCl affords similar mixtures of products.

The yield and selectivity for the desired spiro aminal **26a** can be improved by carrying out the cyclization in $CHCl_3$. Heating **21a** with $Et_3N$ in $CHCl_3$ (12 h, 60 °C) affords 5% of **21a** and 94% of a 20:2:1 mixture of **26a**, **25a**, and **24a**. The change in solvent favors the spiro aminals **24a–26a** at the expense of the dihydropyrimidine **21a** and favors the desired spiro aminal **26a** at the expense of isomers **24a** and **25a**. Furthermore, the 10:6:1 mixture of **26a**, **25a**, and **24a** obtained in methanol is stable for 3 d in $CHCl_3$ at reflux containing either HCl or $Et_3N$, suggesting that the cyclization of **21a** in basic $CHCl_3$ to give **26a** is kinetically controlled. Sprio aminal **26a** should be the major product under kinetically controlled conditions since both new bonds have been formed on the less-hindered face of the dihydropyrimidine. Stereoelectronic preference for pseudoaxial attack, via a chair-like transition state, should also favor the formation of **26a**. The selective formation of the desired stereoisomer **26a** in the cyclization of **21a** in chloroform raises the possibility that the last step in the biosynthesis of crambine B is the nonenzymatic cyclization of crambine C1 (**9**) in a nonpolar environment.

In aqueous solution, dihydropyrimidine **21a** is more stable than spiro aminals **24a–26a**. A mixture of **24a–26a** is quantitatively converted to **21a** on treatment with $K_2CO_3$ in 1:1 $H_2O$–MeOH for 1 d at rt, permitting the recycling of **24a** and **25a**. The solvent effects on the equilibrium between **21a** and **24a–26a** are similar to those in related hydroxy imines in which polar solvents that can hydrogen bond to the alcohol favor the open form.[23]

**Syntheses of the Acyl Portion of Crambine A (23a).** The synthesis of **23a** is completed by reaction of **21a** with MsCl and $Et_3N$ in $CH_2Cl_2$ (30 min, 0 °C, 6 h, rt) to give mesylate **22a**. Reaction of **22a** with $Et_3N$ in $CHCl_3$ (reflux, 12 h) provides 90% of **23a** whose $^1H$ and $^{13}C$ NMR spectra are virtually identical to those reported for the acyl portion of crambine A (**7**). The facile conversion of **21a** to **23a** suggests that crambine C2 is an intermediate in the biosynthesis of crambine A.

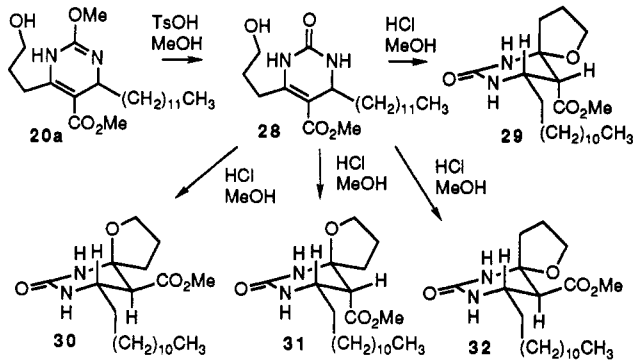
**Syntheses of Cyclic Ureas 28–32.** The use of methoxypyrimidine **20a** as an intermediate facilitates the preparation of the analogous spirocyclic ureas. Toluenesulfonic acid-catalyzed hydrolysis of **20a** in wet MeOH for 16 h at reflux provides 98% of cyclic urea **28** contaminated with a trace of aminals **29–32**. Urea **28** cyclizes in HCl–MeOH (4 d, rt, 10 h, 40 °C) to afford 56% of a 1:6:8:1 mixture of **29**, **30**, **31** and **32**, respectively, and 43% of

(21) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811. Bax, A.; Davis, D. G. *J. Mag. Res.* **1985**, *63*, 207. Two-dimensional phase-sensitive ROESY spectra were obtained on a 500 MHz Bruker AMX-500 spectrometer. Data workup was performed using D. Hare's FELIX program operating on a Silicon Graphics Iris Workstation. Spin-locking periods of 100 and 200 ms were used with a spin-lock field of 2.5 kHz ($\pi/2$ = 100 μs).

(22) Lemieux, R. U.; Bock, K. *Arch. Biochem. Biophys.* **1983**, *221*, 125.

(23) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Plenum: New York, 1985; pp 266–267.

recovered **28**. The stereochemistry of the spirocyclic



products was assigned based on the coupling constants between H-7 and H-13 (**29**, $J$ = 4.1; **30**, $J$ = 11.4; **31**, $J$ = 4.1; **32**, $J$ = 7.4). This establishes that the hydrogens in **30** and **32** are trans and diaxial. The stereochemistry of the aminal center of the ureas is assigned based on mechanistic and $^1$H NMR chemical shift and coupling constant considerations. Mechanistic considerations suggest that the two major urea isomers **30** and **31** should have the same stereochemistry as the major guanidine isomers **25a** and **26a**. In the $^1$H NMR spectra, H-13 absorbs 0.27 ppm downfield in the major isomer **31** ($\delta$ 3.85) as compared to minor isomer **29** ($\delta$ 3.58), since it is deshielded by the axial oxygen.[22] Similarly, H-13 absorbs 0.36 ppm downfield in the major isomer **30** ($\delta$ 3.96) as compared to the minor isomer **32** ($\delta$ 3.60), which has an equatorial oxygen.

The coupling constant between H-7 and H-13 of 11.4 Hz in **30** and 7.4 Hz in **32** provides additional support for the stereochemical assignment. The conformation shown for **30** should be the only populated conformer since the three-carbon substituents are equatorial and the oxygen is axial, which is the preferred orientation due to the anomeric effect. The large coupling constant of 11.4 Hz is consistent with that expected for trans diaxial hydrogens. The conformation shown for **32** should be the major, but not the only populated, conformer since one carbon is axial and the oxygen is equatorial. A ring flip will give a somewhat less stable conformer with two carbons and the oxygen axial. The coupling constant between the diequatorial H-7 and H-13 should be small in this conformer. The observed coupling constant of 7.4 Hz confirms that the conformer shown for **32** is not the only populated conformer.

**Syntheses of Carboxylic Acids 23c and 26c.** Having completed short syntheses of the cyclic moieties of crambines A, B, C1, and C2, we developed procedures for preparation of the natural products with the complete guanidino alkyl ester side chain. There are two fundamentally different approaches that can be taken toward this problem. The most economical approach involves syntheses of the free acids **23c** and **26c** and esterification with the appropriate guanidino alcohol as the last step of the syntheses. This approach would facilitate the preparation of a variety of analogs, such as crambine B with a four carbon side chain or crambine A with a five-carbon side chain. The second approach involves introduction of the guanidino alkyl ester side chain early in the syntheses. Since this approach would make the preparation of analogs more cumbersome, we began by preparing carboxylic acids **23c** and **26c**.

We have been unable to hydrolyze the methyl ester of the bicyclic moieties of crambine A (**23a**) and B (**26a**) to provide the corresponding free acids **23c** and **26c**. This is not surprising since Kashman and Kakisawa were unable to hydrolyze ptilomycalin A to obtain the pentacyclic left half fragment.[1] We therefore decided to repeat the syntheses of **23** and **26** using benzyl acetoacetate to produce benzyl esters **23b** and **26b** by the procedures worked out for the preparation of methyl esters **23a** and **26a**. Hydrogenolysis should give the desired free acids **23c** and **26c**.

Alkylation of the dianion of benzyl acetoacetone with ethylene oxide followed by *in situ* silylation affords 69% of **12b**. Knoevenagel condensation of **12b** with tridecanal affords 84% of **13b** as a 1:1 mixture of stereoisomers. Addition of *O*-methylisourea to **13b** in DMF at 60 °C provides 57% of **19b**. Deprotection of the silyl ether followed by ammonolysis in MeOH yields 40% of **20b** and 54% of a 10:6:1 mixture of **26b**, **25b**, and **24b**. The spirocyclic compounds were reconverted quantitatively to **20b** with $K_2CO_3$ in aqueous methanol. Mesylation of **20b** followed by cyclization affords 80% of **23b**. Cyclization of **20b** with $Et_3N$ in $CHCl_3$ at reflux affords 91% of **26b**. Hydrogenolysis of **23b** and **26b** over 10% Pd/C ($CH_2Cl_2$, 6 h, rt, 1 atm $H_2$) yields the desired free carboxylic acids **23c** (97%) and **26c** (96%), respectively.

With the desired carboxylic acids in hand, we prepared a protected version of the required guanidino alcohols. Reaction of 4-amino-1-butanol with *S*-methylisothiourea gives (4-hydroxybutyl)guanidine (**33a**).[24] (5-Hydroxypentyl)guanidine (**33b**) can be prepared analogously. The guanidine group can be protected as the bis-CBZ derivative using Ottenheijm's one-pot procedure for protection of arginine.[25] Silylation of the alcohol of **33**, reaction with benzyl chloroformate, and acid hydrolysis of the silyl ether gives the bis(CBZ)guanidino alcohols **34a** (76%) and **34b** (66%).

Unfortunately, the free acids **23c** and **26c** proved to be unstable and decarboxylated slowly on storage and during attempted esterification with **33** or **34** under a wide variety of conditions. For instance, attempted esterification of acid **26c** with alcohol **34b** using DCC in HMPA, as described for esterification of other guanidino alcohols,[26] provides 78% of the decarboxylated spirocycle **27**. These results suggests that the free carboxylic acids **23c** and **26c** are not practical intermediates for the syntheses of crambine A and B.

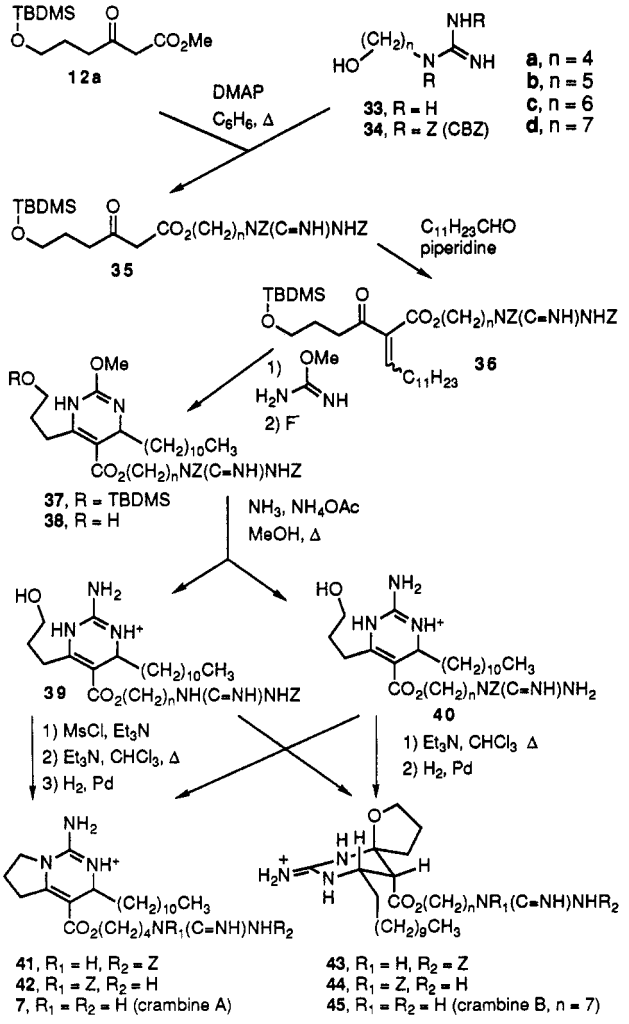
**Synthesis of Crambine A.** We accordingly decided to introduce the guanidino alkyl side chain early in the synthetic sequence prior to construction of the cyclic framework. We were delighted to find that ester exchange by Taber's procedure[27] using DMAP as a catalyst with methyl ester **12a** (2.9 equiv) and guanidino alcohol **34a** gives guanidino alkyl ester **35a** (53%, 92% based on recovered **34a**, 81% based on recovered **12a**). The remainder of the synthesis was carried out analogously to the preparation of the methyl and benzyl esters **23a** and **23b**. Knoevenagel condensation of **35a** with dodecanal

(24) Sterk, G. J.; van der Goot, H.; Timmerman, H. *Arch. Pharm.* **1986**, *319*, 1057.
(25) Jetten, M.; Peters, C. A. M.; van Nispen, J. W. F. M.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1991**, *32*, 6025.
(26) Cheng, K. C.; Yip, C. S.; Yeung, H. W.; Kong, Y. C. *Experientia* **1979**, *35*, 571.
(27) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

provides 82% of **36a**. Addition of *O*-methylisourea to **36a** yields 94% of **37a**. It is noteworthy that this reaction proceeds in much higher yield than with the methyl ester **13a** (79%) or the benzyl ester **13b** (57%). Deprotection of **37a** with aqueous HF in $CH_3CN$ gives 88% of **38a**.

Ammonolysis of **38a**, followed by treatment of the crude mixture of mono- and spirocyclic compounds with $Na_2CO_3$ in aqueous MeOH to cleave any aminal formed, affords 44% of **39a** and 50% of **40a**. Hydrolysis of the first CBZ group takes place under the ammonolysis conditions. The second CBZ group is then less susceptible to hydrolysis. There is little regioselectivity in this hydrolysis. The formation of both **39** and **40** complicates the characterization of intermediates, but is not significant since both can be used for completion of the synthesis. The position of the CBZ is tentatively assigned based on the chemical shift of the methylene group adjacent to the guanidine residue. In **39**, **41**, and **43** the methylene group absorbs upfield at $\delta$ 3.15–3.25. In **40**, **42**, and **44**, in which the CBZ is adjacent to the methylene group, the absorption is shifted downfield to $\delta$ 3.35–3.45.

Mesylation of a mixture of **39a** and **40a** in $CH_2Cl_2$ followed by cyclization of the mesylate with $Et_3N$ in $CHCl_3$ at reflux affords 37% of **41** and 41% of **42**. Hydrogenolysis of **41** over Pd/C in $CHCl_3$ containing HCl provides 93% of crambine A (**7**). A similar hydrogenolysis of **42** yields 92% of crambine A. The $^1H$ and $^{13}C$ NMR spectral data of synthetic crambine A are identical to those of the natural material.[5]



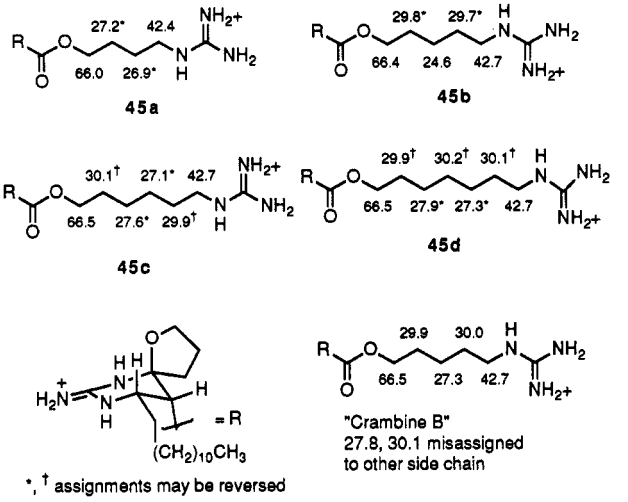




**Figure 1.** $^{13}C$ NMR spectral data for the side chains of **45a–d** and crambine B.

**Synthesis of the Putative Crambine B (45b).** An analogous series of reactions convert **34b** to **45b**, the proposed structure for crambine B. The conversion of **34b** to **39b** and **40b** is identical to the preparation of **39a** and **40a** described above. Heating a solution of **39b** with $Et_3N$ in $CHCl_3$ at reflux for 12 h provides 83% of **43b**. Isomer **44b** is prepared similarly from **40a** in 86% yield. Hydrogenolysis provides **45b** in 90% yield from **43b** and 92% yield from **44b**.

The $^1H$ NMR spectral data of **45b** are virtually identical to those of natural crambine B.[5] The only difference is a multiplet at $\delta$ 1.5 in the spectrum of **45b** that appears at $\delta$ 1.40 in the spectrum of the natural product. These similarities confirm that crambine B has the aminal stereochemistry shown in **45** rather than that originally proposed in 8.

Unfortunately, the $^{13}C$ NMR spectrum of **45b** shows significant differences from that of natural crambine B. The absorptions for the five-carbon side chain of **45b** are shown in Figure 1. These do not correspond well with those assigned to the five-carbon side chain of crambine B. In particular the central carbon of the five-carbon side chain of **45b** absorbs at $\delta$ 24.6 and not $\delta$ 27.3 as reported for natural crambine B. The observed value of $\delta$ 24.6 is very close to that expected since both the guanidine and the carboxylate are $\gamma$ to the central carbon and shield it.[28] Furthermore, carbons 16 and 21 in crambine B are reported to absorb at $\delta$ 27.8 and 30.1, respectively. These assignments are questionable since carbons in the middle of long aliphatic chains typically absorb at $\delta$ 30.6–31.1. There are no absorptions at $\delta$ 27.8 or 30.1 in methyl ester **26a**, benzyl ester **26b**, free acid **26c**, or crambine A (**7**). Therefore the upfield absorption at $\delta$ 27.8, and possibly the absorption at $\delta$ 30.1 as well, is probably due to the guanidino alkyl ester side chain. This analysis and calculations of the chemical shifts[28] suggests that crambine

(28) The effect of the guanidinium ion and the carboxylate ester on the $^{13}C$ NMR absorptions of the side chain carbons was calculated by comparison of the chemical shifts of hexylguanidinium sulfate[29] and hexyl acetate[29] with hexane.[29] For guanidinium the following shifts were calculated: $\alpha$, 26.9, $\beta$, 6.0, $\gamma$, –5.7 and $\delta$, –0.5. For the carboxylate ester the following shifts were calculated: $\alpha$, 50.5, $\beta$, 6.2, $\gamma$, –5.9 and $\delta$, 0. The chemicals shifts for the side chains were calculated by adding these values to those of the appropriate hydrocarbon, butane to heptane. The chemical shifts calculate by this procedure are uniformly 1–2 ppm upfield from the observed values.

B has six or seven, rather than five, carbons in the guanidino alkyl side chain.

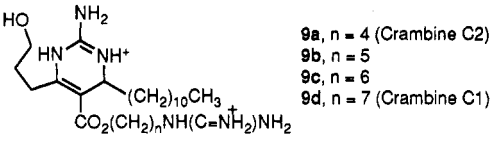
**Synthesis of Crambine B (45d).** We first prepared **45a** with a four-carbon guanidino alkyl side chain since this could be done in two steps from crambine A intermediate **40a**. Cyclization of **40a** with $Et_3N$ in $CHCl_3$ at reflux followed by hydrogenolysis affords 94% of **45a**. The $^{13}C$ NMR absorptions for the four-carbon side chain of **45a** shown in Figure 1 correspond closely to those calculated.[28]

We next prepared **45c** with a six-carbon guanidino alkyl side chain. This synthesis proceeded analogously from (6-hydroxyhexyl)guanidine (**33c**).[24] The spectral data for the six-carbon side chain are much closer to those of crambine B than for the five-carbon side chain (see Figure 1). However, the chemical shifts of the peaks at $\delta$ 27.1 and 27.6 are shifted upfield by 0.2 ppm from crambine B and there is a missing peak near $\delta$ 30.0.

Finally, we prepared **45d** with a seven-carbon guanidino alkyl side chain. 7-Aminoheptanol[30] was converted to **33d** by the literature procedure reported for the lower homologs **33a–c**.[24] The remainder of the synthesis is identical to that described above except that the ammonolysis was carried out on silyl ether **37d**, and the crude product was desilylated with HF in $CH_3CN$ to afford 31% of **39d** and 50% of **40d**. The $^1H$ and $^{13}C$ NMR spectral data for **45d** match those of natural crambine B in all regards except that, as expected, there are two extra carbons in the $\delta$ 30.6–31.1 range of **45d**. Since the molecular weight of natural crambine B was determined by mass spectroscopy, the alkyl side chain of the major congener must have only nine carbons if the guanidino alkyl chain has seven rather than five carbons. Synthetic crambine B (**45d**) with eleven carbons in the alkyl chain is one of the minor congeners of the natural product.[5] These results conclusively establish that crambine B has a seven-carbon rather than a five-carbon guanidino alkyl ester side chain. Rinehart and co-workers have independently established that crambine B has a seven-carbon guanidino alkyl side chain.[31]

**Syntheses of Crambine C1 and C2.** Braekman and co-workers recently reported the isolation of monocyclic crambines C1 and C2 which were proposed to have structures **9b** and **9a** respectively.[6] These natural products are readily available by hydrogenolysis of the monocyclic intermediates **39** and **40**. Hydrogenolysis of **40a** affords 91% of crambine C2 (**9a**) whose $^1H$ NMR spectral data are identical to those reported. Hydrogenolysis of **40d** affords 88% of crambine C1 (**9d**), which can also be prepared in 94% yield by treatment of crambine B (**45d**) with $Na_2CO_3$ in aqueous MeOH for 12 h at rt. The $^1H$ and $^{13}C$ NMR spectral data of synthetic **9d** are virtually identical[32] to those of crambine C1. Therefore, the structure of crambine C1 should also be revised to have a seven-carbon guanidino alkyl side chain.

**Biological Evaluation of the Crambines.** Rinehart found that crambine A and B are cytotoxic to L1210 cells with $IC_{50}$'s of less than 1 $\mu$g/mL.[31] Synthetic racemic crambine A (**7**) and racemic crambine B (**45d**) show identical activity to the natural products.[33] The crambine B analogs **45a–c** with shorter guanidino alkyl side chains are somewhat less active.[33] Synthetic crambine C1 (**9d**) and C2 (**9a**) show comparable activity to crambines A and B in this assay. The methyl esters **23a**, **26a**, and **21a** corresponding to crambines A, B, and C are only a factor of 2–3 less active than the natural product with the complete guanidino alkyl side chain.[33] This suggests that the guanidino alkyl side chain does not play a major role in the biological activity of the crambines.




**9a**, n = 4 (Crambine C2)
**9b**, n = 5
**9c**, n = 6
**9d**, n = 7 (Crambine C1)

**Conclusion.** Crambines A (**7**) (eight steps, 22%), B (**45d**) (eight steps, 19%), C1 (**9d**) (seven steps, 21%), and C2 (**9a**) (seven steps, 27%) have been synthesized expediently and stereospecifically by a biomimetic route from methyl acetoacetate. Aminodihydropyrimidines **39** and **40** are formed efficiently from enone ester **36** by a two-step procedure involving addition of *O*-methylisourea to give methoxydihydropyrimidine **38** followed by displacement of the methoxy group of **38** with ammonia. Hydrogenolysis of **40a** and **40d** affords crambines C2 and C1, respectively. Mesylation of the alcohol of **39a** or **40a** followed by $Et_3N$-catalyzed cyclization and hydrogenolysis affords crambine A (**7**). Aminal formation from **39d** or **40d** in $CHCl_3$ followed by hydrogenolysis proceeds stereospecifically to provide crambine B (**45d**). The structure of crambine B has been revised to the stereochemistry shown in **45** and both crambines B and C1 have a seven- rather than five-carbon guanidino alkyl chain. The methods developed here should be applicable to the syntheses of the more complex targets ptilomycalin A and the crambescidins.

## Experimental Section

**General Procedures.** NMR spectra were recorded at 300 MHz in $CDCl_3$ except where otherwise indicated. Chemical shifts are reported in $\delta$ (ppm) and coupling constants in hertz. IR spectra are reported in $cm^{-1}$. Combustion analyses were performed by Baron Consulting Co. and Spang Microanalytical Laboratory. Reactions were run under nitrogen.

**Methyl 6-[(*tert*-Butyldimethylsilyl)oxy]-3-oxohexanoate (12a).** A solution of LDA (42 mmol) was prepared under $N_2$ by adding *n*-BuLi (16.8 mL, 2.5 M, 42 mmol) to diisopropylamine (5.8 mL, 4.25 g, 42 mmol) in 50 mL of THF at 0 °C and stirring for 0.5 h. Methyl acetoacetate (2.3 mL, 2.32 g, 20 mmol) was added slowly at 0 °C. The solution was stirred for 1 h and ethylene oxide (1.0 mL, 0.8 g, 20 mmol) was added at 0 °C. The solution was stirred for 2 h and a solution of *t*-butyldimethylsilyl chloride (3.2 g, 21 mmol) in 20 mL of THF was added. The mixture was stirred at rt for 12 h, treated with 30 mL of HCl (1.2 M), and extracted with $Et_2O$ (3 × 50 mL). The organic layers were washed

(29) *Sadtler Standard Carbon-13 NMR Spectra*; Sadtler Research Laboratories: Philadelphia; hexylguanidinium sulfate, 20638; hexyl acetate, 606; pentane, 1830; hexane, 126; heptane, 414.

(30) McKay, A. F.; Skulski, M.; Garmaise, D. L.; *Can. J. Chem.* **1958**, *36*, 147.

(31) Jares-Erijman, E. A.; Sakai, R.; Ingrum, A.; Carney, J. R.; Rinehart, K. L. *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO, Spring 1993; American Chemical Society, Washington, DC, 1993; ORGN 250.

(32) The only difference is that there is an absorption at $\delta$ 32.8 in crambine C1 assigned to C-10 that is not present in the spectrum of **9d**. C-10 absorbs at $\delta$ 32.3 in **9d** and the protected analogues **39** and **40**. The absorption at $\delta$ 32.3 in crambine C-1 is misassigned to C-17.

(33) The % inhibition of L1210 cells (0.5, 1.0, 2.0, and 3.0 $\mu$g/mL): natural crambine A (10, 92, 100, 100), synthetic crambine A (**7**) (10, 90, 100, 100), methyl ester **23a** corresponding to crambine A (0, 40, 80, 96), natural crambine B (0, 60, 92, 96), synthetic crambine B (**45d**) (0, 50, 90, 95), **45c** (0, 10, 80, 90), **45b** (0, 10, 80, 90), **45a** (0, 10, 94, 92), methyl ester **26a** corresponding to crambine B (0, 0, 40, 88), synthetic crambine C1 (**9d**) (40, 80, 99, 100), synthetic crambine C2 (**9a**) (0, 80, 92, 99), methyl ester **21a** corresponding to crambine C (0, 0, 40, 95). We thank Prof. Rinehart and Dr. Jares-Erijman for the obtaining the biological activity data.

with water (3 × 20 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (10:1 hexane–EtOAc) gave 3.16 g (58%) of **12a** as a colorless oil: $^1$H NMR 3.74 (s, 3), 3.62 (t, 2, $J$ = 6.1), 3.47 (s, 2), 2.63 (t, 2, $J$ = 7.2), 1.81 (tt, 2, $J$ = 7.2, 6.1), 0.88 (s, 9), 0.03 (s, 6); $^{13}$C NMR 202.5, 167.6, 61.8, 52.2, 49.0, 39.4, 26.5, 25.8 (3 C), 18.2, –5.5 (2 C); IR (neat) 2965, 2940, 2870, 1760, 1725, 1660, 1640, 1475, 1465, 1440, 1325, 1260, 1100, 1005, 970, 835. The data are identical to the literature data.[14]

**Methyl (*E*)- and (*Z*)-2-[4-[(*tert*-Butyldimethylsilyl)oxy]-1-oxobutyl]-2-pentadecenoate (13a*E* and 13a*Z*).** A solution of ester **12a** (1.00 g, 3.65 mmol), tridecanal (0.75 g, 3.79 mmol), and piperidine (3 drops) in 30 mL of benzene was stirred at rt for 1 h under $N_2$. The solution was heated to 80 °C and half of the solvent was distilled out to remove water azeotropically. An additional drop of piperidine was added and the mixture was stirred at rt for 12 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 hexane–EtOAc) gave 1.46 g (88%) of **13a** as a 1:1.1 mixture of double bond isomers. Anal. Calcd for $C_{28}H_{50}O_4Si$: C, 68.67; H, 11.08. Found: C, 68.81; H, 10.94.

Careful flash chromatography of 50 mg of the mixture on silica gel (25:1 hexane–EtOAc) gave 14.1 mg of pure **13a*E*** followed by 27.3 mg of a mixture rich in **13a*Z*** and 8.0 mg of pure **13a*Z***.

The data for **13a*E***: $^1$H NMR 6.92 (t, 1, $J$ = 7.9), 3.77 (s, 3), 3.64 (t, 2, $J$ = 6.2), 2.72 (t, 2, $J$ = 7.3), 2.18 (dt, 2, $J$ = 7.9, 7.4), 1.84 (tt, 2, $J$ = 6.2, 7.3), 1.45 (m, 2), 1.16–1.40 (m, 18), 0.89 (s, 9), 0.88 (t, 3, $J$ = 6.7), 0.04 (s, 6); $^{13}$C NMR 203.7, 165.0, 148.6, 135.3, 62.0, 52.1, 40.0, 31.9, 29.6 (3 C), 29.47, 29.44, 29.33, 29.30, 29.26, 28.60, 26.7, 25.9 (3 C), 22.7, 18.3, 14.1, –5.3 (2 C); IR (neat) 2925, 2855, 1735, 1720, 1640, 1465, 1435, 1250, 1100, 830, 770.

The data for **13a*Z***: $^1$H NMR 6.86 (t, 1, $J$ = 7.7), 3.83 (s, 3), 3.63 (t, 2, $J$ = 6.1), 2.72 (t, 2, $J$ = 7.3), 2.29 (dt, 2, $J$ = 7.7, 7.4), 1.82 (tt, 2, $J$ = 7.3, 6.1), 1.49 (m, 2), 1.20–1.40 (m, 18), 0.89 (s, 9), 0.88 (t, 3, $J$ = 6.7), 0.04 (s, 6); $^{13}$C NMR 197.4, 167.1, 148.1, 136.6, 62.0, 52.0, 35.4, 31.9, 30.0, 29.6 (4 C), 29.47, 29.31, 29.26, 28.4, 27.0, 25.9 (3 C), 22.7, 18.3, 14.1, –5.4 (2 C); IR (neat) 2930, 2860, 1740, 1700, 1620, 1465, 1435, 1250, 1205, 1100, 830, 770.

**2-Amino-6-dodecyl-5-[4-[(*tert*-butyldimethylsilyl)oxy]-1-oxobutyl]-5,6-dihydro-4(1*H*)-pyrimidinone Hydrochloride (17).** A solution of guanidine (0.11 mmol) in 8 mL of *t*-BuOH was prepared by stirring a mixture of guanidinium carbonate (11 mg, 0.06 mmol) and *t*-BuOK (12.3 mg, 0.11 mmol) in 8 mL of *t*-BuOH at 50 °C for 4 h and filtration under $N_2$ to remove $K_2CO_3$. Enone ester **13a** (52.0 mg, 0.11 mmol) was added to the solution which was stirred at rt for 5 h under $N_2$. The solvent was removed under reduced pressure and the residue was treated with 5 mL of 2 M HCl and brine (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were washed with brine (3 × 10 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 EtOAc–MeOH) gave 42.0 mg (71%) of **17**: $^1$H NMR 3.88 (m, 1), 3.60 (t, 2, $J$ = 6.2), 3.36 (d, 1, $J$ = 6.8), 2.74 (dt, 1, $J$ = 18.0, 6.9), 2.65 (dt, 1, $J$ = 18.0, 6.9), 1.78 (m, 2), 1.10–1.55 (m, 22), 0.89 (s, 9), 0.88 (t, 3, $J$ = 6.7), 0.03 (s, 6); $^{13}$C NMR 206.2, 175.5, 160.3, 62.0, 57.9, 50.1, 39.7, 34.2, 31.9, 29.7 (2 C), 29.6, 29.5, 29.4, 29.2, 26.6, 26.1, 25.9 (3 C), 25.2, 22.7, 18.3, 14.1, –5.3 (2 C); IR (neat) 3500–3000, 2965, 2855, 1720, 1670, 1620, 1520, 1470, 1420, 1300, 1255, 1100, 830, 770.

**Methyl 6-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-4-dodecyl-1,4-dihydro-2-methoxypyrimidine-5-carboxylate (19a).** A suspension of **13a** (200 mg, 0.44 mmol), $NaHCO_3$ (250 mg, 2.98 mmol), and *O*-methylisourea sulfate (200 mg, 0.81 mmol) in DMF (4 mL) was stirred at 60 °C for 12 h. The mixture was treated with brine (20 mL) and extracted with $Et_2O$ (3 × 25 mL). The organic layers were washed with brine (10 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 hexane–EtOAc) gave 178 mg (79%) of **19a** as a colorless oil: $^1$H NMR 4.49 (t, 1, $J$ = 5.7), 3.79 (s, 3), 3.67 (s, 3), 3.66 (t, 2, $J$ = 6.0), 2.87 (dt, 1, $J$ = 13.4, 6.7), 2.68 (dt, 1, $J$ = 13.4, 7.1), 1.77 (ddt, 2, $J$ = 7.1, 6.7, 6.0), 1.45 (m, 2), 1.10–1.40 (m, 20), 0.90 (s, 9), 0.86 (t, 3, $J$ = 6.7), 0.07 (s, 6); $^{13}$C NMR 167.0, 153.4, 152.4, 101.9, 62.3, 54.4, 53.2, 50.9, 36.9, 31.9, 30.2, 29.6 (5 C), 29.4, 29.3, 28.2, 25.9 (3 C), 24.2, 22.6, 18.3, 14.1, –5.4 (2 C); IR (neat) 3340, 2940, 2860, 1710, 1625, 1555, 1470, 1440, 1310, 1240, 1190, 1100, 1020, 960, 835, 775. Anal. Calcd for $C_{28}H_{54}N_2O_4Si$: C, 65.83; H, 10.66. Found: C, 65.91; H, 10.37.

**Methyl 4-Dodecyl-1,4-dihydro-6-(3-hydroxypropyl)-2-methoxypyrimidine-5-carboxylate (20a).** A solution of ester **19a** (170 mg, 0.33 mmol) and tetrabutylammonium fluoride (150 mg, 0.57 mmol) in 20 mL of THF was stirred at rt for 12 h. The mixture was treated with brine (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layers were washed with brine (15 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (3:2 hexane–EtOAc) gave 118.6 mg (90%) of **20a** followed by 5.6 mg (4%) of **28**.

The data for **20a**: $^1$H NMR 4.41 (dd, 1, $J$ = 7.5, 3.4), 3.80 (s, 3), 3.71 (s, 3), 3.64 (t, 2, $J$ = 5.7), 2.94 (dt, 1, $J$ = 13.0, 6.6), 2.75 (dt,1, $J$ = 13.0, 6.7), 1.86 (m, 2), 1.05–1.55 (m, 22), 0.88 (t, 3, $J$ = 6.7); $^{13}$C NMR 167.5, 157.3, 156.0, 103.9, 61.0, 54.3, 52.2, 51.1, 36.9, 31.9, 30.2, 30.1, 29.6 (4 C), 29.55, 29.40, 29.32, 24.1, 22.7, 14.1; IR (neat) 3650–3000, 2940, 2860, 1700, 1620, 1555, 1510, 1460, 1435, 1305, 1240, 1190, 1135, 1095, 1015, 950. Anal. Calcd for $C_{22}H_{40}N_2O_4$: C, 66.62; H, 10.17. Found: C, 66.69; H, 9.88.

**Methyl 2-Amino-4-dodecyl-1,4-dihydro-6-(3-hydroxypropyl)pyrimidine-5-carboxylate Hydrochloride (21a).** A solution of **20a** (100 mg) and $NH_4OAc$ (30 mg) in 20 mL of MeOH was saturated with $NH_3$ at 0 °C for 5 min. The mixture was sealed and heated at 60 °C for 2 d. The solvent was removed under reduced pressure, and the residue was treated with brine and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layers were washed with brine (2 × 15 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (92:8 $CH_2Cl$–MeOH) gave 38.9 mg (37%) of a 1:6:10 mixture of **24a**, **25a**, and **26a**, followed by 63.8 mg (61%) of **21a** as a glassy oil which was crystallized from hexane at –20 °C: mp 74.0–75.0 °C; $^1$H NMR 10.08 (br s, 1), 8.81 (br d, 1, $J$ = 2.6), 7.65 (br s, 2), 4.41 (dt, 1, $J$ = 2.6, 5.9), 3.75 (s, 3), 3.67 (t, 2, $J$ = 5.5), 2.98 (dt, 1, $J$ = 13.5, 6.8), 2.82 (dt, 1, $J$ = 13.5, 7.0), 1.90 (m, 2), 1.56 (m, 2), 1.05–1.50 (m, 20), 0.88 (t, 3, $J$ = 6.7); $^{13}$C NMR 165.2, 152.6, 147.5, 104.5, 60.7, 51.8, 50.0, 36.3, 31.9, 30.6, 29.7, 29.65 (3 C), 29.42, 29.34, 29.1, 27.3, 24.2, 22.7, 14.1; IR (neat) 3500–3000, 2925, 2855, 1700, 1655, 1555, 1435, 1350, 1245, 1185, 1090. Anal. Calcd for $C_{21}H_{40}N_3O_3Cl$: C, 60.34; H, 9.65. Found: C, 60.00; H, 10.01.

A similar reaction of **20a** (85.0 mg) in MeOH (20 mL) saturated with $NH_3$ at 0 °C in the absence of $NH_4OAc$ at 60 °C for 3 d gave less than 5% of **21a** and 95% of recovered **20a**.

**Methyl 1-Amino-3,5,6,7-tetrahydro-3-dodecylpyrrolo[1,2-*c*]pyrimidine-4-carboxylate Hydrochloride (23a).** Methanesulfonyl chloride (6.1 μL, 9.0 mg, 0.078 mmol) was added to a solution of **21a** (30 mg, 0.072 mmol) and $Et_3N$ (20 μL, 14.5 mg, 0.12 mmol) in 3 mL of $CH_2Cl_2$ at 0 °C. The mixture was stirred at 0 °C for 0.5 h and at rt for 6 h. Removal of the solvent under reduced pressure gave crude **22a**. A solution of crude **22a** and $Et_3N$ (2 drops) was heated at reflux in 5 mL of $CHCl_3$ for 12 h, treated with brine (10 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were washed with brine (2 × 10 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 EtOAc–MeOH) gave 26.8 mg (90%) of **23a** as a white solid: mp 104.0–105.0 °C; $^1$H NMR ($CD_3OD$) 4.38 (t, 1, $J$ = 5.9), 3.81 (ddd, 1, $J$ = 2.8, 9.9, 9.5), 3.75 (s, 3), 3.66 (ddd, 1, $J$ = 7.3, 9.5, 9.5), 3.32 (ddd, 1, $J$ = 18.0, 8.4, 3.0), 2.96 (ddd, 1, $J$ = 18.0, 9.3, 9.3), 2.23 (m, 1), 2.09 (m, 1), 1.56 (m, 2), 1.10–1.45 (m, 20), 0.89 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 166.9, 153.3, 153.1, 103.4, 52.4, 51.6, 49.3, 37.7, 33.4, 32.1, 31.07, 31.04 (2 C), 30.96, 30.87, 30.77, 30.6, 25.4, 24.0, 23.2, 14.7; IR (neat) 3500–3000, 2925, 2855, 1700, 1680, 1620, 1550, 1435, 1385, 1350, 1270, 1190, 1105, 1090. Anal. Calcd for $C_{21}H_{38}N_3O_2Cl$: C, 63.06; H, 9.58. Found: C, 63.11; H, 9.83.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1$H, $J$; $^{13}$C) OMe (3.75; 52.4), C-6 (166.9), C-7 (103.4), C-8 (153.1), $H_2C$-9 (2.96 ddd, 9.3/9.3/18.0 and 3.32 ddd, 3.0/8.4/18.0; 32.1), $H_2C$-10 (2.09 m and 2.23 m; 23.2), $H_2C$-11 (3.66 ddd, 7.3/9.1/9.3 and 3.81 ddd, 2.9/9.1/9.1; 49.3), C-12 (153.3), HC-13 (4.38 dd, 5.9/5.9; 51.6), $H_2C$-14 (1.56 m; 37.7), $H_2C$-15 (1.45 m; 25.4), $H_2C$-16 to $H_2C$-22 (1.2–1.4 m; 31.07, 31.04, 31.04, 30.96, 30.87, 30.77, 30.6), $H_2C$-23 (1.2–1.4 m; 33.4), $H_2C$-24 (1.2–1.4 m; 24.0), $H_2C$-25 (0.89 t, 6.7; 14.7).

**Methyl (5α,9α,10α)-, (5α,9β,10α)-, and (5α,9β,10β)-7-Amino-9-dodecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate Hydrochloride (24a, 25a, and 26a).** A solution of **21a** (28 mg) and concd HCl (3 drops) in 20 mL of MeOH was heated to 40 °C for 4 d. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (92:8 $CH_2Cl_2$–MeOH) gave 10.9 mg (39%) of a 1:6:10 mixture of **24a**, **25a**, and **26a** followed by 16.8 mg (60%) of unreacted **21a**. Careful flash chromatography of 62 mg of the mixture of **24a**, **25a**, and **26a** on silica gel (95:5 EtOAc–MeOH) gave 6.5 mg of pure **26a** followed by 25.0 mg of a mixture rich in **26a** and 26.0 mg of a mixture rich in **25a**. Careful chromatography of the third fraction (26.0 mg) obtained above on silica gel (96:4 $CH_2Cl_2$–MeOH) gave 2.8 mg of pure **25a** followed by 23.0 mg of a mixture rich in **25a**.

A solution of **21a** (30.0 mg) and $Et_2N$ (2 drops) in 15 mL of $CHCl_3$ was refluxed for 12 h under $N_2$. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (92:8 $CH_2Cl_2$–MeOH) gave 28.2 mg (94%) of a 20:2:1 mixture of **26a**, **25a**, and **24a**, followed by 1.5 mg (5%) of unreacted **21a**.

A 1:6:10 mixture of **24a**, **25a** and **26a** was stable in either acidic (TsOH or HCl) or basic ($Et_3N$) $CHCl_3$ at reflux for 2–3 d. A trace of **21a** was formed, but the ratio of **26a** to **25a** changed very slightly, if at all. A 1:4:5 mixture of **24a–26a** is converted to a 1:3:5 mixture by heating in $CHCl_3$ and $Et_3N$ for 3 d. This indicates that the cyclization of **21a** in $CHCl_3$ is kinetically controlled. A 1:6:10 mixture of **24a**, **25a** and **26a** reverts to a 60:40 mixture of **21a** and **24a–26a** on heating in MeOH containing $Et_3N$. These reactions were run with 10 mg of substrate in 15–20 mL of solvent and 1 drop of concd HCl, 1 drop of $Et_3N$, or 3 mg of $TsOH·H_2O$.

Reaction of **21a** (10 mg) with 1 drop of concd HCl in MeOH (3 mL) for 3 days gave 45% of **21a** and 55% of a 1:6:10 mixture of **24a–26a** as determined by analysis of the $^1H$ NMR spectrum. An identical reaction starting with 8.0 mg of a 1:8:10 mixture of **24a–26a** gave 40% of **21a** and 60% of a 1:6:10 mixture of **24a–26a**. The higher concentration may be responsible for the slightly different ratios of **21a**:**24a–26a** in these experiments. Equilibration in MeOH is much faster with $Et_3N$ than with HCl.

Reaction of a mixture of **24a–26a** with $K_2CO_3$ in 1:1 $H_2O$–MeOH for 1 d at rt or with NaOH in 1:1 $H_2O$–THF for 12 h at reflux gives **21a** quantitatively without hydrolysis of the ester.

The data for **24a** were determined from mixtures: $^1H$ NMR ($CD_3OD$) 4.06 (m, 1), 3.92 (m, 1), 3.69 (s, 3), 3.69 (m, 1), 3.10 (d, 1, $J$ = 4.0), 2.0–2.2 (m, 4), 1.55 (m, 2), 1.2–1.4 (m, 20), 0.90 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 170.3, 155.0, 92.7, 70.6, 52.5, 51.8, 50.4, 41.5, 33.4, 33.3, 31.05, 30.94, 30.89, 30.78, 30.78, 30.78, 30.69, 26.8, 25.6, 24.0, 14.7.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from reference 5: ($^1H$, $J$, $^{13}C$) OMe (3.69; 52.5), C-6 (170.3), HC-7 (3.10 d, 4.0; 50.4), C-8 (92.7), $H_2C$-9 (2.0–2.2 m; 41.5), $H_2C$-10 (2.0–2.2 m; 25.6), $H_2C$-11 (3.92 m and 4.06 m; 70.6), C-12 (155.0), HC-13 (3.69 m; 51.8), $H_2C$-14 (1.55 m; 33.3), $H_2C$-15 (1.2–1.4 m; 26.8), $H_2C$-16 to $H_2C$-22 (1.2–1.4 m; 31.05, 30.94, 30.89, 30.78, 30.78, 30.78, 30.69), $H_2C$-23 (1.2–1.4 m; 33.4), $H_2C$-24 (1.2–1.4 m; 24.0), $H_2C$-25 (0.90 t, 6.7; 14.7).

The data for **25a**: $^1H$ NMR ($CD_3OD$) 3.80–4.00 (m, 3), 3.76 (s, 3), 2.92 (d, 1, $J$ = 11.5), 2.49 (m, 1), 2.00–2.16 (m, 2), 1.82 (m, 1), 1.10–1.65 (m, 22), 0.89 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 170.5, 155.1, 90.4, 70.0, 53.3, 51.8, 50.5, 36.5, 34.2, 33.4, 31.1 (2 C), 30.94, 30.87, 30.78, 30.67, 30.64, 26.3, 25.7, 24.0, 14.7; IR (neat) 3500–3300, 2960, 2855, 1750, 1675, 1620, 1460, 1435, 1260, 1190, 1155, 1040, 920. Anal. Calcd for $C_{21}H_{40}N_3O_3Cl$: C, 60.34; H, 9.65. Found: C, 60.06; H, 9.73.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1H$, $J$, $^{13}C$) OMe (3.76; 51.8), C-6 (170.5), HC-7 (2.92 d, 11.5; 50.5*), C-8 (90.4), $H_2C$-9 (2.0–2.4 m; 36.5), $H_2C$-10 (1.8–2.3 m; 25.7), $H_2C$-11 (3.80–4.00 m; 70.0), C-12 (155.1), HC-13 (3.95 m; 53.3*), $H_2C$-14 (1.55 m; 34.2), $H_2C$-15 (1.2–1.4 m; 36.8), $H_2C$-16 to $H_2C$-22 (1.2–1.4 m; 31.1, 31.1, 30.94, 30.87, 30.78, 30.67, 30.64), $H_2C$-23 (1.2–1.4 m; 33.4), $H_2C$-24 (1.2–1.4 m; 24.0), $H_2C$-25 (0.89 t, 6.7; 14.7). The ROESY spectrum shows intense cross peaks between H-7 and H-9 and no cross peak between H-9 and H-13.

The data for **26a**: $^1H$ NMR ($CD_3OD$) 4.02 (m, 1), 3.92 (m, 1), 3.85 (ddd, 1, $J$ = 4.3, 7.3, 7.3), 3.72 (s, 3), 3.00 (d, 1, $J$ = 4.2), 2.00–2.40 (m, 4), 1.56 (m, 2), 1.47 (m, 2), 1.15–1.40 (m, 18), 0.89 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 170.5, 155.4, 90.2, 69.2, 52.8, 50.4, 49.8, 36.4, 33.4, 33.0, 31.05, 31.02, 30.89, 30.76 (3 C), 30.65, 26.7, 26.0, 24.0, 14.7; IR (neat) 3500–3300, 2920, 2850, 1745, 1675, 1620, 1460, 1440, 1200, 1160, 1030, 920. Anal. Calcd for $C_{21}H_{40}N_3O_3Cl$: C, 60.34; H, 9.65. Found: C, 60.39; H, 9.60.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1H$, $J$, $^{13}C$) OMe (3.72; 52.8), C-6 (170.5), HC-7 (3.00 d, 4.2; 49.8), C-8 (90.2), $H_2C$-9 (2.10 m; 36.4), $H_2C$-10 (2.1–2.3 m; 26.0), $H_2C$-11 (3.92 m and 4.02 m; 69.2), C-12 (155.4), HC-13 (3.85 ddd, 4.2/7.3/7.3; 50.4), $H_2C$-14 (1.55 m; 33.0), $H_2C$-15 (1.2–1.4 m; 26.7), $H_2C$-16 to $H_2C$-22 (1.2–1.4 m; 31.05, 31.02, 30.89, 30.76, 30.76, 30.76, 30.65), $H_2C$-23 (1.2–1.4 m; 33.4), $H_2C$-24 (1.2–1.4 m; 24.0), $H_2C$-25 (0.89 t, 6.7; 14.7).

Two-dimensional phase-sensitive ROESY spectra were obtained on a 500-MHz Bruker AMX-500 spectrometer. Data workup was performed using D. Hare's FELIX program operating on a Silicon Graphics Iris Workstation. Spin-locking periods of 100 and 200 ms were used with a spin-lock field of 2.5 kHz ($\pi/2$ = 100 μs). The ROESY spectra show intense cross peaks between H-7 and H-9 and H-7 and H-13 in both **24a** and **26a**. The ROESY spectra show an intense cross peak between H-9 and H-13 in the minor isomer **24a** but not in the major isomer **26a**.

**1-Amino-3,5,6,7-tetrahydro-3-dodecylpyrrolo[1,2-*c*]pyrimidine-4-carboxylic Acid Hydrochloride (23c)** was prepared in 97% yield as described below for **26c**. **23c**: $^1H$ NMR ($CD_3OD$) 4.38 (t, 1, $J$ = 5.8), 3.79 (dt, 1, $J$ = 2.8, 9.4), 3.64 (dt, 1, $J$ = 7.5, 9.4), 3.34 (ddd, 1, $J$ = 3.3, 8.5, 18.0), 2.95 (dt, 1, $J$ = 18.0, 9.1), 2.20 (m, 1), 2.09 (m, 1), 1.58 (m, 2), 1.15–1.50 (m, 20), 0.89 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 168.8, 153.3, 151.6, 105.1, 52.0, 50.1, 37.7, 33.4, 31.9, 31.09, 31.06 (2 C), 30.99, 30.92, 30.8, 30.7, 25.5, 24.0, 23.3, 14.7; IR (neat) 2400–3600, 2923, 2852, 1691, 1679, 1655, 1611, 1546, 1455, 1427, 1384, 1265, 1192, 1096.

**(5α,9β,10β)-7-Amino-9-dodecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylic Acid Hydrochloride (26c).** A suspension of **26b** (44 mg) and palladium on powdered charcoal (10%, 40 mg) in 8 mL of $CH_2Cl_2$ was stirred at rt under hydrogen for 6 h and filtered. The residue was washed with $CHCl_3$–MeOH (1:1). The combined filtrates were dried and concentrated under reduced pressure to give crude **26c** (34.5 mg, 96%): $^1H$ NMR ($CD_3OD$) 4.01 (m, 1), 3.91 (m, 1), 3.83 (dt, 1, $J$ = 4.0, 7.1), 2.88 (d, 1, $J$ = 3.9), 2.02–2.22 (m, 4), 1.63 (m, 2), 1.48 (m, 2), 1.20–1.42 (m, 18), 0.90 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 171.7, 155.4, 90.2, 69.1, 50.1, 49.9, 36.4, 33.4, 33.1, 31.05 (3 C), 30.9, 30.8 (2 C), 30.7, 26.8, 26.0, 24.0, 14.7; IR (neat) 2500–3500, 2923, 2853, 2731, 1672, 1620, 1465, 1403, 1352, 1285, 1203, 1053.

**(5α,9β)-7-Amino-9-dodecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene Hydrochloride (27).** A solution of **26c** (34.5 mg, 0.087 mmol), DCC (32 mg, 0.15 mmol), and (5-hydroxypentyl)-guanidinium toluenesulfonate[24] (44 mg, 0.14 mmol) in 1.5 mL of HMPA was stirred at rt for 3 d, treated with brine (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried and concentrated under reduced pressure. Flash chromatography of the residue on silica gel gave 24.0 mg (78%) of **27** as a colorless oil: $^1H$ NMR 8.89 (br s, 1), 8.13 (br s, 1), 7.03 (br s, 2), 4.00 (dt, 1, $J$ = 6.1, 8.0), 3.88 (dt, 1, $J$ = 6.1, 7.3), 3.61 (m, 1), 2.27 (m, 1), 2.15 (m, 1), 1.80–2.10 (m, 2), 1.93 (dd, 1, $J$ = 12.7, 5.4), 1.66 (t, 1, $J$ = 12.7), 1.40–1.64 (m, 2), 1.05–1.40 (m, 20), 0.88 (t, 3, $J$ = 6.7); $^{13}C$ NMR 154.2, 87.9, 67.4, 47.3, 37.4, 36.9, 34.8, 31.9, 29.66, 29.62 (2 C), 29.58, 29.44, 29.37, 29.33, 25.2, 24.6, 22.7, 14.1; IR (neat) 3000–3600, 2923, 2853, 1668, 1614, 1465, 1352, 1269, 1192, 1024.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]butan-1-ol (34a).** This procedure was adapted from a procedure for the protection of arginine.[25] Trimethylsilyl chloride (1.95 mL, 15.0 mmol) was slowly added to a suspension of (4-hydroxybutyl)guanidinium toluenesulfonate (1.51 g, 5.0 mmol) (prepared from 4-amino-1-butanol and *S*-methylthioisourea sulfate)[24] and DIPEA (3.5 mL, 20 mmol) in 20 mL of 1,2-dichloroethane at rt. The mixture was warmed to 40 °C for 1 h and then cooled to 0 °C. DIPEA (2.68 mL, 15 mmol) followed by benzyl chloroformate (1.9 mL, 15 mmol) were then added. The mixture was stirred for 20 min at 0 °C and for 40 h at rt, treated with 30 mL of 1 M HCl, and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were washed with brine (20 mL) and dried ($Na_2SO_4$). Removal of the solvent

under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 $CH_2Cl_2$–MeOH) gave 1.83 g (76%) of **34a** as a white solid: mp 62.0–63.0 °C; $^1H$ NMR 9.46 (br s, 1), 9.28 (br s, 1), 7.28–7.45 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 3.98 (t, 2, $J$ = 7.6), 3.64 (t, 2, $J$ = 6.1), 1.71 (tt, 2, $J$ = 7.6, 6.8), 1.51 (tt, 2, $J$ = 6.8, 6.1); $^{13}C$ NMR 163.6, 160.5, 155.8, 136.8, 134.6, 128.79, 128.74, 128.35 (2 C), 128.23 (2 C), 127.72 (2 C), 127.69 (2 C), 68.9, 66.8, 61.7, 44.1, 28.7, 24.8; IR (KBr) 3150–3600, 3065, 3035, 2945, 2870, 1720, 1645, 1610, 1510, 1455, 1405, 1380, 1245, 1190, 1175, 1095, 1000, 905, 805, 770, 740, 695. Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.85; H, 6.32; N, 10.57.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]butyl 6-[(*tert*-Butyldimethylsilyl)oxy]-3-oxohexanoate (35a).** A solution of **12a** (400 mg, 1.46 mmol, 2.9 equiv), **34a** (200 mg, 0.5 mmol), and DMAP (15 mg, 0.12 mmol) in 30 mL of benzene was heated at reflux for 24 h. Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (7:3 hexane–EtOAc) gave 310 mg (77%) of recovered **12a**, followed by 170 mg (53%, 81% based on recovered **12a**, 92% based on recovered **34a**) of **35a**, followed by 85 mg of **34a** (1:1 hexane–EtOAc).

The data for **35a**: $^1H$ NMR 9.45 (br s, 1), 9.27 (br s, 1), 7.25–7.45 (m, 10), 5.25 (s, 2), 5.14 (s, 2), 4.08 (t, 2, $J$ = 6.1), 4.01 (t, 2, $J$ = 6.7), 3.60 (t, 2, $J$ = 6.1), 3.39 (s, 2), 2.57 (t, 2, $J$ = 7.2), 1.78 (tt, 2, $J$ = 6.1, 7.2), 1.55–1.70 (m, 4), 0.88 (s, 9), 0.03 (s, 6); $^{13}C$ NMR 202.6, 167.1, 163.8, 160.5, 155.8, 136.9, 134.6, 128.77, 128.73 (2 C), 128.3 (2 C), 128.2 (2 C), 127.85 (2 C), 127.75, 68.8, 66.9, 64.8, 61.8, 49.1, 44.1, 39.4, 26.5, 25.9 (3 C), 25.6, 25.2, 18.2, –5.4 (2 C); IR (neat) 3389, 3276, 3065, 3033, 2953, 2856, 1740, 1716, 1644, 1611, 1513, 1450, 1407, 1379, 1256, 1200, 1101, 1008, 906, 836, 777, 750, 698. Anal. Calcd for $C_{33}H_{47}N_3O_8Si$: C, 61.75; H, 7.38; N, 6.55. Found: C, 61.51; H, 7.59; N, 6.54.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]butyl (*E*)- and (*Z*)-2-[4-[(*tert*-Butyldimethylsilyl)oxy]-1-oxobutyl]-2-tetradecenoate (36a*E* and 36a*Z*).** A solution of **35a** (0.58 g, 0.90 mmol), dodecanal (0.66 g, 3.6 mmol), and piperidine (25 mg, 0.3 mmol) in 10 mL of $CH_2Cl_2$ was cooled to –20 °C for 3 d, diluted with hexane (20 mL), washed with $H_2O$ (20 mL, containing one drop of HOAc) and brine (10 mL), and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (17:3 hexane–EtOAc) gave 0.60 g (82%) of **36a** as a 1:1 mixture of double bond isomers followed by 80 mg of recovered **35a** (7:3 hexane–EtOAc). The double bond isomers **36a*E*** and **36a*Z*** were separated by flash chromatography on silica gel (9:1 hexane–EtOAc).

The data for **36a**: IR (neat) 3388, 3272, 3065, 3033, 2926, 2855, 1720, 1643, 1611, 1512, 1455, 1406, 1378, 1254, 1200, 1101, 1008, 906, 836, 776, 697. Anal. Calcd for $C_{45}H_{69}N_3O_8Si$: C, 66.88; H, 8.61; N, 5.20. Founfd: C, 66.51; H, 8.61; N, 4.90.

The data for **36a*E***: $^1H$ NMR 9.46 (br s, 1), 9.28 (br s, 1), 7.25–7.43 (m, 10), 6.87 (t, 1, $J$ = 8.0), 5.25 (s, 2), 5.14 (s, 2), 4.12 (t, 2, $J$ = 8.0), 4.01 (m, 2), 3.61 (t, 2, $J$ = 6.2), 2.68 (t, 2, $J$ = 7.4), 2.16 (dt, 2, $J$ = 8.0, 7.6), 1.81 (m, 2), 1.55–1.73 (m, 4), 1.44 (m, 2), 1.15–1.40 (m, 16), 0.876 (s, 9), 0.88 (t, 3, $J$ = 6.7), 0.030 (s, 6); $^{13}C$ NMR 203.6, 164.3, 163.8, 160.46, 155.81, 148.1, 136.8, 135.4, 134.56, 128.79, 128.74 (2 C), 128.31 (4 C), 128.24 (2 C), 127.7, 68.87, 66.9, 64.6, 61.99, 44.09, 40.0, 31.8, 29.6 (3 C), 29.42, 29.39, 29.30, 29.25, 28.6, 26.7, 25.9 (3 C), 25.63, 25.23, 22.6, 18.2, 14.1, –5.4 (2 C).

The data for **36a*Z***: $^1H$ NMR 9.46 (br s, 1), 9.28 (br s, 1), 7.25–7.43 (m, 10), 6.83 (t, 1, $J$ = 8.1), 5.25 (s, 2), 5.14 (s, 2), 4.18 (t, 2, $J$ = 6.0), 4.03 (m, 2), 3.61 (t, 2, $J$ = 6.2), 2.69 (t, 2, $J$ = 7.3), 2.25 (dt, 2, $J$ = 8.1, 7.4), 1.80 (m, 2), 1.55–1.75 (m, 4), 1.45 (m, 2), 1.15–1.40 (m, 16), 0.879 (s, 9), 0.88 (t, 3, $J$ = 6.7), 0.033 (s, 6); $^{13}C$ NMR 197.3, 166.5, 163.8, 160.48, 155.79, 147.5, 136.9, 136.8, 134.60, 128.74, 128.31 (2 C), 128.24 (4 C), 127.8 (2 C), 127.7, 68.84, 66.9, 64.7, 61.93, 44.13, 35.1, 31.8, 30.0, 29.6 (3 C), 29.42, 29.30, 29.25, 28.4, 27.0, 25.9 (3 C), 25.69, 25.28, 22.6, 18.2, 14.1, –5.4 (2 C).

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]butyl 6-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-1,4-dihydro-2-methoxy-4-undecylpyrimidine-5-carboxylate (37a).** A suspension of **36a** (580 mg, 0.72 mmol), *O*-methylisourea sulfate (560 mg, 2.3 mmol), and $NaHCO_3$ (400 mg, 4.8 mmol) in 6 mL of DMF was stirred at 55 °C for 3 h, treated with $H_2O$ (10 mL), and extracted with hexane–EtOAc (2:1, 3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 hexane–EtOAc) gave 0.58 g (94%) of **37a** as a colorless oil: $^1H$ NMR 7.22–7.45 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 4.49 (t, 1, $J$ = 5.5), 3.95–4.10 (m, 4), 3.81 (s, 3), 3.65 (t, 2, $J$ = 6.0), 2.86 (dt, 1, $J$ = 13.2, 6.7), 2.67 (dt, 1, $J$ = 13.2, 6.8), 1.77 (m, 2), 1.53–1.75 (m, 4), 1.46 (m, 2), 1.15–1.40 (m, 18), 0.91 (s, 9), 0.88 (t, 3, $J$ = 6.6), 0.08 (s, 6); $^{13}C$ NMR 166.3, 163.8, 160.5, 155.9, 153.3, 152.2, 136.9, 134.6, 128.7 (3 C), 128.3 (2 C), 128.2 (2 C), 127.8 (2 C), 127.7, 101.9, 68.8, 67.0, 63.3, 62.3, 54.4, 53.3, 44.3, 37.0, 31.9, 30.1, 29.68, 29.63 (4 C), 29.60, 29.3, 28.1, 25.9 (3 C), 25.5, 24.3, 22.6, 18.3, 14.1, –5.4 (2 C); IR (neat) 3386, 3065, 3033, 2926, 2854, 1720, 1699, 1648, 1612, 1548, 1513, 1455, 1379, 1252, 1199, 1100, 1008, 906, 836, 777, 697. Anal. Calcd for $C_{47}H_{73}N_5O_8Si$: C, 65.32; H, 8.51; N, 8.10. Found: C, 65.09; H, 8.59; N, 7.90.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]butyl 1,4-Dihydro-6-(3-hydroxypropyl)-2-methoxy-4-undecylpyrimidine-5-carboxylate (38a).** A solution of **37a** (215 mg, 0.25 mmol) and aqueous HF (50%, 300 mg) in 8 mL of $CH_3CN$ was stirred at rt for 1.5 h, treated with brine (10 mL) and aqueous ammonium hydroxide (25%, 2 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (1:1 hexane–EtOAc) gave 152 mg (88%) of **38a** as a colorless oil: $^1H$ NMR 9.46 (br s, 1), 9.28 (br s, 1), 7.26–7.45 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 4.35 (dd, 1, $J$ = 5.7, 4.4), 3.95–4.12 (m, 4), 3.79 (s, 3), 3.59 (t, 2, $J$ = 5.7), 2.90 (dt, 1, $J$ = 13.2, 6.4), 2.70 (dt, 1, $J$ = 13.2, 6.6), 1.82 (m, 2), 1.55–1.73 (m, 4), 1.10–1.50 (m, 20), 0.88 (t, 3, $J$ = 6.7); $^{13}C$ NMR 166.8, 163.8, 160.4, 158.8, 155.9, 155.8, 136.8, 134.6, 128.78, 128.74 (2 C), 128.36 (2 C), 128.18 (2 C), 127.9 (2 C), 127.8, 103.7, 68.9, 67.0, 63.6, 61.0, 54.7, 52.2, 44.3, 37.0, 31.8, 30.4, 29.6 (5 C), 29.5, 29.3, 25.9, 25.6, 24.2, 22.6, 14.1; IR (neat) 3385, 3275, 3065, 3033, 2926, 2854, 1720, 1697, 1647, 1612, 1549, 1513, 1454, 1379, 1250, 1198, 1100, 1008, 907, 777, 697. Anal. Calcd for $C_{41}H_{59}N_5O_8$: C, 65.66; H, 7.93; N, 9.34. Found: C, 65.25; H, 7.77; N, 8.92.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-amino]butyl 2-Amino-1,4-dihydro-6-(3-hydroxypropyl)-4-undecylpyrimidine-5-carboxylate Hydrochloride (39a) and 4-[*N*-(Iminoaminomethyl)-*N*-[(phenylmethoxy)carbonyl]-amino]butyl 2-Amino-1,4-dihydro-6-(3-hydroxypropyl)-4-undecylpyrimidine-5-carboxylate Hydrochloride (40a).** A solution of **38a** (148 mg, 0.20 mmol) and $NH_4OAc$ (40 mg, 0.5 mmol) in 20 mL of *tert*-butanol was saturated with $NH_3$ at 10 °C for 5 min and heated in a sealed tube at 60 °C for 3 d. The solvent was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (20 mL), and the residual solid was separated by filtration. Removal of the solvent under reduced pressure gave a light yellow oil. A solution of the oil and $Na_2CO_3$ (20 mg) in 10 mL of MeOH–$H_2O$ (2:1) was stirred at rt for 12 h to convert any spirocyclic compound to **39a** and **40a**. MeOH was removed under reduced pressure and the mixture was treated with brine (10 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (92:8 $CH_2Cl_2$–MeOH) gave 56 mg (44%) of **39a** followed by 63 mg (50%) of **40a** (85:15 $CH_2Cl_2$–MeOH).

The data for **39a**: $^1H$ NMR 8.82 (br s, 1), 8.3 (br s, 2), 7.60 (br s, 1), 7.27–7.40 (m, 5), 5.22 (s, 2), 5.00–5.14 (m, 3), 4.39 (t, 1, $J$ = 5.5), 4.14 (t, 2, $J$ = 6.1), 3.63 (t, 2, $J$ = 5.6), 3.21 (m, 2), 2.92 (dt, 1, $J$ = 13.2, 6.6), 2.77 (dt, 1, $J$ = 13.2, 6.7), 1.86 (m, 2), 1.68 (m, 2), 1.40–1.68 (m, 4), 1.18–1.40 (m, 18), 0.87 (t, 3, $J$ = 6.7); $^{13}C$ NMR 164.7, 156.1, 152.9, 152.6, 147.4, 134.0, 128.9, 128.7 (2 C), 128.5 (2 C), 104.5, 68.9, 64.3, 60.7, 50.0, 40.5, 36.3, 31.9, 30.6, 29.6 (3 C), 29.4, 29.3, 29.2, 27.4, 26.7, 25.9, 24.2, 22.6, 14.1; IR (neat) 3000–3600, 2925, 2854, 1692, 1620, 1553, 1454, 1248, 1145, 1087, 776, 735, 697. Anal. Calcd for $C_{32}H_{53}N_6O_5Cl$: C, 60.31; H, 8.38; N, 13.19. Found: C, 60.62; H, 8.44; N, 12.85.

The data for **40a**: $^1H$ NMR ($CDCl_3$ and 5 drops of $CD_3OD$) 7.25–7.40 (m, 5), 5.23 (s, 2), 4.41 (t, 1, $J$ =

11.2, 5.6), 4.14 (dt, 1, $J$ = 11.2, 5.5), 3.63 (t, 2, $J$ = 5.8), 3.42 (m, 2), 2.88 (dt, 1, $J$ = 13.4, 6.6), 2.74 (dt, 1, $J$ = 13.4, 6.7), 1.65–1.90 (m, 6), 1.54 (m, 2), 1.15–1.50 (m, 18), 0.87 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CDCl_3$ and 5 drops of $CD_3OD$) 164.9, 153.7, 153.3, 152.0, 147.6, 134.0, 128.8, 128.6 (2 C), 128.3 (2 C), 104.1, 68.8, 63.9, 60.8, 49.8, 41.4, 36.1, 31.7, 30.6, 29.5 (3 C), 29.4, 29.2 (2 C), 27.7, 25.6, 25.0, 24.0, 22.5, 13.9; IR (neat) 3000–3500, 2923, 2854, 1747, 1694, 1633, 1556, 1504, 1392, 1241, 1156, 1087, 910, 735. Anal. Calcd for $C_{32}H_{53}N_6O_5Cl$: C, 60.31; H, 8.38; N, 13.19. Found: C, 60.62; H, 8.12; N, 12.40.

**4-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-amino]butyl 1-Amino-3,5,6,7-tetrahydro-3-undecylpyrrolo-[1,2-*c*]pyrimidine-4-carboxylate Hydrochloride (41) and 4-[*N*-(Iminoaminomethyl)-*N*-[(phenylmethoxy)carbonyl]-amino]butyl 1-Amino-3,5,6,7-tetrahydro-3-undecylpyrrolo-[1,2-*c*]pyrimidine-4-carboxylate Hydrochloride (42).** Methanesulfonyl chloride (20 mg, 0.18 mmol) in 1 mL of $CH_2Cl_2$ was slowly added to a solution of a 0.9:1 mixture of **39a** and **40a** (100 mg, 0.16 mmol) and $Et_3N$ (30 mg, 0.3 mmol) in 5 mL of $CH_2Cl_2$ at 0 °C. The solution was stirred for 15 min at 0 °C and for 3 h at rt, treated with brine (10 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried ($Na_2SO_4$). Removal of the solvent gave an oil, which was heated in 15 mL of $CHCl_3$ and $Et_3N$ (2 drops) at reflux for 24 h. The mixture was treated with brine (15 mL). The $CHCl_3$ layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (92:8 $CH_2Cl_2$–MeOH) gave 36 mg (37%) of **41** followed by 40 mg (41%) of **42**.

The data for **41**: $^1$H NMR ($CD_3OD$) 7.25–7.45 (m, 5), 5.07 (s, 2), 4.39 (t, 1, $J$ = 5.8), 4.19 (m, 2), 3.80 (ddd, 1, $J$ = 2.7, 9.1, 9.1), 3.65 (ddd, 1, $J$ = 7.4, 9.0, 9.1), 3.29 (ddd, 1, $J$ = 3.0, 8.8, 18.4), 3.15 (t, 2, $J$ = 6.7), 2.96 (ddd, 1, $J$ = 9.1, 9.1, 18.4), 2.20 (m, 1), 2.09 (m, 1), 1.70 (m, 2), 1.45–1.68 (m, 4), 1.10–1.50 (m, 18), 0.89 (t, 3, $J$ = 6.5); $^{13}$C NMR ($CD_3OD$) 166.4, 159.5, 159.2, 153.3, 152.9, 138.7, 129.7 (2 C), 129.2, 129.0 (2 C), 103.7, 67.6, 65.8, 51.6, 49.3, 41.6, 37.7, 33.4, 32.2, 31.05 (2 C), 30.98, 30.89, 30.76, 30.61, 27.9, 27.3, 25.4, 24.0, 23.2, 14.7; IR (neat) 3000–3500, 2925, 2853, 1692, 1679, 1630, 1547, 1454, 1397, 1346, 1262, 1193, 1092, 1026, 738, 697. Anal. Calcd for $C_{32}H_{51}N_6O_4Cl$: C, 62.07; H, 8.30. Found: C, 62.30; H, 8.17.

The data for **42**: $^1$H NMR ($CD_3OD$) 7.26–7.52 (m, 5), 5.27 (s, 2), 4.41 (t, 1, $J$ = 5.9), 3.82 (ddd, 1, $J$ = 2.9, 9.1, 9.1), 3.67 (ddd, 1, $J$ = 7.4, 9.1, 9.5), 3.38 (t, 2, $J$ = 6.5), 3.30 (ddd, 1, $J$ = 18.4, 9.2, 2.9), 2.98 (ddd, 1, $J$ = 18.4, 9.3, 9.3), 2.22 (m, 1), 2.12 (m, 1), 1.63–1.84 (m, 4), 1.57 (m, 2), 1.10–1.43 (m, 18), 0.89 (t, 3, $J$ = 6.8); $^{13}$C NMR ($CD_3OD$) 166.4, 155.5, 154.9, 153.3, 153.1, 136.5, 130.1, 130.0 (2 C), 129.9 (2 C), 103.5, 70.1, 65.4, 51.6, 49.3, 42.7, 37.8, 33.4, 32.3, 31.05, 31.00 (2 C), 30.9, 30.8, 30.7, 27.3, 26.3, 25.5, 24.0, 23.2, 14.8; IR (neat) 3000–3600, 2924, 2854, 1745, 1693, 1682, 1651, 1552, 1455, 1397, 1347, 1240, 1196, 1156, 1109, 1091, 943, 910, 771, 744, 698. Anal. Calcd for $C_{32}H_{53}N_6O_5Cl$: C, 62.07; H, 8.30; N, 13.57. Found: C, 62.31; H, 8.41; N, 13.15.

**4-[(Aminoiminomethyl)amino]butyl 1-Amino-3,5,6,7-tetrahydro-3-undecylpyrrolo[1,2-*c*]pyrimidine-4-carboxylate Hydrochloride (7, Crambine A).** A suspension of **41** (25 mg), palladium on charcoal (10%, 30 mg), and aqueous HCl (37%, 1 drop) in 10 mL of $CHCl_3$ was stirred at rt under $H_2$ for 3 h and filtered through Celite and silica gel. The residue was washed with $CHCl_3$–MeOH (1:1). Concentration of the combined filtrates under reduced pressure followed by flash chromatography of the residue on silica gel (9:1 $CHCl_3$–MeOH) gave 18.2 mg (93%) of crambine A (**7**). Crambine A was prepared in 92% yield from **42** by the same procedure: $^1$H NMR ($CD_3OD$) 4.41 (t, 1, $J$ = 5.3, $H_{13}$), 4.22 (t, 2, $J$ = 5.8, $H_5$), 3.83 (ddd, 1, $J$ = 2.7, 9.1, 9.1, $H_{11}$), 3.69 (ddd, 1, $J$ = 6.4, 9.0, 9.1, $H_{11}$), 3.33 (ddd, 1, $J$ = 3.1, 9.0, 18.1, $H_9$), 3.24 (t, 2, $J$ = 6.8, $H_2$), 3.01 (ddd, 1, $J$ = 9.0, 9.0, 18.1, $H_9$), 2.25 (m, 1, $H_{10}$), 2.13 (m, 1, $H_{10}$), 1.60–1.90 (m, 4, $H_3$ and $H_4$), 1.57 (m, 2, $H_{14}$), 1.20–1.50 (m, 18, $H_{15}$ to $H_{23}$), 0.89 (t, 3, $J$ = 6.5, $H_{24}$); $^{13}$C NMR ($CD_3OD$) 166.4, 158.9, 153.3, 153.0, 103.6, 65.5, 51.6, 49.3, 42.4, 37.8, 33.4, 32.3, 31.03 (2 C), 30.98, 30.89, 30.75, 30.65, 27.3, 27.0, 25.5, 24.0, 23.3, 14.7; IR (neat) 3000–3600, 2924, 2853, 1676, 1656, 1622, 1549, 1460, 1400, 1348, 1268, 1198, 1090.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1$H, $J$, $^{13}$C) C-1 (158.9), $H_2$C-2 (3.24 t, 6.8; 42.4), $H_2$C-3 (1.70 m; 27.0), $H_2$C-4 (1.80 m; 27.3), $H_2$C-5 (4.22 m; 65.5), C-6 (166.4), C-7 (103.6), C-8 (153.0), $H_2$C-9 (3.01 ddd, 9.0/9.0/18.1 and 3.33 ddd, 3.1/9.0/18.1; 32.3), $H_2$C-10 (2.13 m and 2.25 m; 23.3), $H_2$C-11 (3.69 ddd, 6.4/9.0/9.1 and 3.83 ddd, 2.7/9.1/9.1; 49.3), C-12 (155.3), HC-13 (4.41 t, 5.3; 51.6), $H_2$C-14 (1.57 m; 37.8), $H_2$C-15 (1.42 m; 25.5), $H_2$C-16 to $H_2$C-21 (1.20–1.40 m; 31.03, 31.03, 30.98, 30.89, 30.75, 30.65), $H_2$C-22 (1.20–1.40 m; 33.4), $H_2$C-23 (1.20–1.40 m; 24.0), $H_2$C-24 (0.89 t, 6.7; 14.7). The data are identical to the literature data.[5]

**4-[(Aminoiminomethyl)amino]butyl (5α,9β,10β)-7-Amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate Hydrochloride (45a).** A solution of **40a** (18 mg) and $Et_3N$ (3 drops) in 10 mL of $CHCl_3$ was heated at reflux for 12 h. The mixture was cooled to rt, and palladium on charcoal (10%, 30 mg) and aqueous HCl (35%, 1 drop) were added. The mixture was stirred at rt under $H_2$ for 3 h and filtered through Celite. The filtrate was washed with brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (17:3 $CHCl_3$–MeOH) gave 14.0 mg (94%) of **45a** as a colorless oil: $^1$H NMR ($CD_3OD$) 4.19 (m, 2), 4.03 (m, 1), 3.93 (m, 1), 3.86 (dt, 1, $J$ = 4.2, 7.3), 3.22 (t, 2, $J$ = 6.8), 2.99 (d, 1, $J$ = 4.2), 2.05–2.23 (m, 4), 1.62–1.80 (m, 4), 1.40–1.60 (m, 4), 1.20–1.40 (m, 16), 0.90 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 158.9, 155.4, 90.1, 69.2, 66.0, 50.3, 50.2, 42.4, 36.5, 33.4, 33.0, 31.0 (2 C), 30.9, 30.83, 30.78, 30.70, 27.2, 26.9, 26.8, 26.0, 24.0, 14.7; IR (neat) 3000–3550, 2923, 2853, 1730, 1665, 1650, 1620, 1465, 1392, 1379, 1280, 1253, 1037; HRFABMS $m/e$ for $C_{24}H_{47}N_6O_3$ (M + H)$^+$ calcd 467.3710, found 467.3719.

**5-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]pentan-1-ol (34b).** A mixture of *S*-methylisothiourea sulfate (3.0 g, 10.7 mmol) and 5-aminopentan-1-ol (2.1 g, 20 mmol) in 40 mL of MeOH was heated at reflux for 2 d. The solvent was removed under reduced pressure, and sodium toluenesulfonate (3.9 g, 20 mmol) and 1,2-dichloroethane (50 mL) were added to the residue. The resulting mixture was stirred at 50 °C for 1 h and then cooled to rt. DIPEA (15 mL, 80 mmol) was added and trimethylsilyl chloride (8 mL, 60 mmol) was slowly added to the mixture at rt. The mixture was stirred at 40 °C for 2 h and cooled to 0 °C, and DIPEA (11 mL, 60 mmol) was added. Benzyl chloroformate (8 mL, 60 mmol) was added to the mixture in one portion at 0 °C. The mixture was stirred for 20 min at 0 °C and at rt for 4 h and treated with 60 mL of 1 M HCl. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 40 mL). The combined organic layers were washed with $H_2O$ (30 mL) and brine (30 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (17:3 $CH_2Cl_2$–MeOH) gave 5.5 g (66%) of **34b** as a white solid: mp 70.0–71.0 °C; $^1$H NMR 9.44 (br s, 1), 9.28 (br s, 1), 7.25–7.45 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 3.98 (t, 2, $J$ = 7.5), 3.55 (t, 2, $J$ = 6.5), 1.60 (m, 2), 1.52 (m, 2), 1.31 (m, 2); $^{13}$C NMR 163.9, 160.6, 156.0, 137.0, 134.7, 128.79, 128.74 (2 C), 128.4 (2 C), 128.30 (2 C), 127.9 (2 C), 127.8, 68.8, 67.0, 62.6, 44.6, 32.1, 28.3, 22.7; IR (KBr) 3539, 3498, 3398, 3264, 3090, 3063, 3032, 2938, 2860, 1720, 1652, 1613, 1510, 1496, 1452, 1399, 1379, 1323, 1289, 1253, 1237, 1178, 1099, 1012, 911, 782, 744, 696. Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.63; H, 6.67; N, 10.22.

**5-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-amino]pentyl (5α,9β,10β)-7-Amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate Hydrochloride (43b).** A solution of **39b** (30 mg) and $Et_3N$ (2 drops) in 10 mL of $CHCl_3$ was heated at reflux for 12 h, treated with brine (15 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine (15 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel (19:1 $CH_2Cl_2$–MeOH) gave 25 mg (83%) of **43b**: $^1$H NMR ($CD_3OD$) 7.23–7.45 (m, 5), 5.06 (s, 2), 4.13 (t, 2, $J$ = 6.4), 4.01 (m, 1), 3.90 (m, 1), 3.84 (ddd, 1, $J$ = 4.3, 7.4, 7.4), 3.12 (t, 2, $J$ = 6.9), 2.97 (d, 1, $J$ = 4.1), 2.00–2.22 (m, 4), 1.65 (m, 2), 1.20–1.58 (m, 24), 0.89 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 159.2, 155.3 (2 C), 138.7, 129.7 (2 C), 129.2, 129.0 (2 C), 90.1, 69.2, 67.6, 66.4, 50.3, 50.0, 41.9, 36.4, 33.4, 33.1, 31.05 (2 C), 30.94, 30.83, 30.78 (2 C), 30.72, 29.6, 26.8, 26.0, 24.6,

24.0, 14.8; IR (neat) 3300–3600, 2926, 2854, 1728, 1673, 1620, 1531, 1464, 1455, 1360, 1248, 1164, 1029, 723, 697.

**5-[*N*-[Iminoaminomethyl]-*N*-[(phenylmethoxy)carbonyl]-amino]pentyl (5α,9β,10β)-7-amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate hydrochloride (44b)** was prepared in 86% yield analogously from **40b**: $^1$H NMR ($CD_3OD$) 7.25–7.45 (m, 5), 5.28 (s, 2), 4.17 (t, 2, $J$ = 6.3), 4.02 (m, 1), 3.92 (m, 1), 3.85 (ddd, 1, $J$ = 4.2, 7.3, 7.3), 3.38 (t, 2, $J$ = 7.1), 2.97 (d, 1, $J$ = 4.2), 2.03–2.25 (m, 4), 1.40–1.78 (m, 8), 1.15–1.40 (m, 18), 0.89 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 155.4, 155.3, 154.7, 136.4, 130.1, 130.0 (2 C), 129.9 (2 C), 90.1, 70.2, 69.2, 66.3, 50.3, 50.2, 43.1, 36.4, 33.3, 33.0, 31.0 (2 C), 30.9, 30.76, 30.73, 30.66, 29.6, 29.1, 26.7, 26.0, 24.6, 24.0, 14.7; IR (neat) 3000–3600, 2925, 2854, 1732, 1682, 1673, 1633, 1621, 1504, 1456, 1359, 1240, 1157, 1032, 746, 722, 698. Anal. Calcd for $C_{33}H_{55}N_6O_5Cl$: C, 60.86; H, 8.51. Found: C, 60.86; H, 8.35.

**5-[(Aminoiminomethyl)amino]pentyl (5α,9β,10β)-7-amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate hydrochloride (45b)** was prepared in 92% yield from **44b** and 90% yield from **43b** by hydrogenolysis as described above for **7**: $^1$H NMR ($CD_3OD$) 4.16 (t, 2, $J$ = 6.5), 4.03 (m, 1), 3.93 (m, 1), 3.86 (ddd, 1, $J$ = 4.3, 7.3, 7.3), 3.21 (m, 2), 2.98 (d, 1, $J$ = 4.2), 2.02–2.23 (m, 4), 1.68 (m, 2), 1.61 (m, 2), 1.42–1.54 (m, 4), 1.20–1.42 (m, 18), 0.90 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 158.9, 155.4, 90.1, 69.2, 66.4, 50.3, 50.2, 42.7, 36.4, 33.4, 33.1, 31.04 (2 C), 30.93, 30.81, 30.77, 30.71, 29.8, 29.7, 26.8, 26.0, 24.6, 24.0, 14.7; IR (neat) 3000–3650, 2924, 2854, 1731, 1668, 1650, 1621, 1465, 1393, 1377, 1359, 1283, 1251, 1176, 1039, 722; HRFABMS $m/e$ for $C_{25}H_{49}N_6O_3$ (M + H)$^+$ calcd for 481.3866, found 481.3848.

**6-[(Aminoiminomethyl)amino]hexyl (5α,9β,10β)-7-amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate hydrochloride (45c)** was prepared in 86% yield from **39c** and 88% of yield from **40c** as described above for **45a**: $^1$H NMR ($CD_3OD$) 4.16 (t, 2, $J$ = 6.5), 4.02 (m, 1), 3.93 (m, 1), 3.85 (ddd, 1, $J$ = 4.3, 7.4, 7.4), 3.18 (m, 2), 2.97 (d, 1, $J$ = 4.2), 2.00–2.25 (m, 4), 1.50–1.74 (m, 6), 1.38–1.50 (m, 4), 1.20–1.38 (m, 18), 0.90 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 158.9, 155.4, 90.1, 69.2, 66.45, 50.3, 50.2, 42.7, 36.4, 33.4, 33.1, 31.05 (2 C), 30.92, 30.80, 30.77, 30.72, 30.1, 29.9, 27.6, 27.1, 26.8, 26.0, 24.0, 14.8; IR (neat) 3000–3650, 2924, 2854, 1731, 1670, 1621, 1465, 1360, 1283, 1251, 1176, 1036, 722; HRFABMS $m/e$ $C_{26}H_{51}N_6O_3$ (M + H)$^+$ calcd 495.4023, found 495.3996.

**7-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-*N*-[(phenylmethoxy)carbonyl]amino]heptan-1-ol (34d)** was prepared in 61% yield from 7-amino-1-heptanol hydrochloride[30] as described above for **34b** except that sodium hydroxide (1 equiv) and 7-amino-1-heptanol hydrochloride were heated at 50 °C for 30 min before *S*-methylisothiourea sulfate was added: mp 63.0–64.0 °C; $^1$H NMR 9.44 (br s, 1), 9.28 (br s, 1), 7.28–7.42 (m, 10), 5.24 (s, 2), 5.15 (s, 2), 3.97 (t, 2, $J$ = 7.6), 3.58 (t, 2, $J$ = 6.6), 1.57 (m, 2), 1.49 (m, 2), 1.18–1.40 (m, 6); $^{13}$C NMR 163.8, 160.5, 155.9, 136.9, 134.7, 128.66, 128.64 (2 C), 128.3 (2 C), 128.1 (2 C), 127.8 (2 C), 127.7, 68.7, 66.9, 62.7, 44.7, 32.5, 28.8, 28.5, 26.4, 25.4; IR (KBr) 3395, 3278, 3090, 3066, 3034, 2928, 2862, 1719, 1654, 1634, 1519, 1498, 1440, 1385, 1251, 1231, 1205, 1178, 1108, 1098, 1079, 1008, 933, 916, 871, 851, 809, 747, 730, 697. Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.52. Found: C, 65.55; H, 7.37; N, 9.50.

**7-[*N*-[Imino[[(phenylmethoxy)carbonyl]amino]methyl]-amino]heptyl 2-Amino-1,4-dihydro-6-(3-hydroxypropyl)-4-undecylpyrimidine-5-carboxylate Hydrochloride (39d) and 7-[*N*-(Iminoaminomethyl)-*N*-[(phenylmethoxy)carbonyl]-amino]heptyl 2-Amino-1,4-dihydro-6-(3-hydroxypropyl)-4-undecylpyrimidine-5-carboxylate Hydrochloride (40d).** A mixture of **37d** (500 mg, 0.61 mmol) and $NH_4OAc$ (150 mg, 2.0 mmol) in 25 mL of *tert*-butanol, which was saturated with $NH_3$ at 10 °C for 10 min, was heated in a sealed tube at 60 °C for 2 d. The solvent was removed under reduced pressure, the residue was dissolved in $CH_2Cl_2$ (30 mL), and the solid $NH_4OAc$ was removed by filtration. Removal of $CH_2Cl_2$ under reduced pressure gave a light yellow oil, which was dissolved in 20 mL of $CH_3CN$–HF (19:1) and stirred for 2 h. The mixture was treated with brine (containing 2% of $NH_4OH$, 30 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure followed by flash chromatography of the residue on silica gel gave 116 mg (31%) of **39d** (19:1 $CH_2Cl_2$–MeOH) and 187 mg (50%) of **40d** (9:1 $CH_2Cl_2$–MeOH).

The data for **39d**: $^1$H NMR ($CDCl_3$) 8.78 (br s, 1), 7.65 (br s, 1), 7.26–7.40 (m, 5), 5.09 (s, 2), 4.87 (br t, 1, $J$ = 5.8, NH), 4.40 (m, 1), 4.13 (m, 2), 3.65 (t, 2, $J$ = 5.6), 3.18 (dt, 2, $J$ = 6.8, 5.8), 2.96 (dt, 1, $J$ = 13.4, 7.0), 2.80 (dt, 1, $J$ = 13.4, 6.9), 1.90 (m, 2), 1.64 (m, 2), 1.42–1.60 (m, 4), 1.15–1.45 (m, 24), 0.87 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CDCl_3$) 164.8, 156.4, 152.6 (2 C), 147.2, 136.6, 128.5 (2 C), 128.1 (3 C), 104.8, 66.6, 64.8, 60.6, 50.1, 41.0, 36.3, 31.9, 30.6, 29.9 (3 C), 29.6, 29.4, 29.3, 29.2, 28.8, 28.5, 27.3, 26.6, 26.0, 24.2, 22.7, 14.1; IR (neat) 3000–3520, 2926, 2854, 1693, 1555, 1455, 1244, 1089. Anal. Calcd for $C_{35}H_{59}N_6O_5Cl$: C, 61.88; H, 8.75. Found: C, 61.58; H, 9.20.

The data for **40d**: $^1$H NMR ($CD_3OD$) 7.32–7.46 (m, 5), 5.27 (s, 2), 4.42 (t, 1, $J$ = 5.7), 4.18 (m, 2), 3.62 (t, 2, $J$ = 6.3), 3.33 (t, 2, $J$ = 7.1), 2.86 (dt, 1, $J$ = 13.0, 7.4), 2.77 (dt, 1, $J$ = 13.0, 6.4), 1.83 (m, 2), 1.61–1.75 (m, 4), 1.57 (m, 2), 1.15–1.52 (m, 24), 0.89 (t, 3, $J$ = 6.6); $^{13}$C NMR ($CD_3OD$) 166.3, 155.2, 154.7, 153.7, 149.1, 136.4, 130.1, 130.0 (2 C), 129.9 (2 C), 106.2, 70.1, 66.1, 62.4, 51.3, 43.2, 37.3, 33.3, 32.3, 31.0 (2 C), 30.9, 30.8, 30.7, 30.5, 30.1, 29.9, 29.4, 29.0, 27.8, 27.3, 25.4, 24.0, 14.8; IR (neat) 3000–3580, 2925, 2854, 1745, 1691, 1634, 1558, 1498, 1456, 1240, 1154, 1089. Anal. Calcd for $C_{35}H_{59}N_6O_5Cl$: C, 61.88; H, 8.75. Found: C, 61.48; H, 9.26.

**7-[(Aminoiminomethyl)amino]heptyl (5α,9β,10β)-7-amino-9-undecyl-1-oxa-6,8-diazaspiro[4.5]dec-7-ene-10-carboxylate hydrochloride (45d, crambine B)** was prepared in 89% yield from **43d** and 91% yield from **44d** as described above for the preparation of **45a**: $^1$H NMR ($CD_3OD$) 4.15 (m, 2), 4.02 (m, 1), 3.92 (m, 1), 3.85 (ddd, 1, $J$ = 4.3, 7.3, 7.3), 3.17 (t, 2, $J$ = 7.1), 2.97 (d, 1, $J$ = 4.2), 2.02–2.23 (m, 4), 1.67 (m, 2), 1.60 (m, 2), 1.55 (m, 2), 1.20–1.50 (m, 22), 0.90 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 170.0, 158.9, 155.4, 90.1, 69.2, 66.5, 50.3, 50.2, 42.7, 36.4, 33.4, 33.1, 31.0 (2 C), 30.9, 30.77, 30.76, 30.71, 30.2, 30.1, 29.9, 27.9, 27.3, 26.8, 26.0, 24.0, 14.7; IR (neat) 3000–3600, 2925, 2854, 1731, 1672, 1620, 1465, 1359, 1283, 1176, 1034; HRFABMS $m/e$ $C_{27}H_{53}N_6O_3$ (M + H)$^+$ calcd 509.4179, found 509.4177.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1$H, $J$, $^{13}$C) C-1 (158.9), $H_2C$-2 (3.17 t, 7.1; 42.7), $H_2C$-3 (1.60 m; 30.1), $H_2C$-3A (1.20–1.50 m; 27.3), $H_2C$-3B (1.20–1.50 m; 29.9), $H_2C$-3C (1.20–1.50 m; 27.9), $H_2C$-4 (1.67 m; 30.2), $H_2C$-5 (4.15 m; 66.5), C-6 (170), HC-7 (2.97 d, 4.2; 50.2), C-8 (90.1), $H_2C$-9 (2.08 m; 36.4), $H_2C$-10 (2.08 m and 2.19 m; 26.0), $H_2C$-11 (3.92 m and 4.02 m; 69.2), C-12 (155.4), HC-13 (3.85 ddd, 4.2/7.3/7.3; 50.3), $H_2C$-14 (1.55 m; 33.1), $H_2C$-15 (1.20–1.50 m; 26.8), $H_2C$-16 to $H_2C$-21 (1.20–1.50 m; 31.0, 31.0, 30.9, 30.77, 30.76, 30.71), $H_2C$-22 (1.20–1.50 m; 33.4), $H_2C$-23 (1.20–1.50 m; 24.0), $H_2C$-24 (0.90 t, 6.7; 14.7). The spectral data are identical to the literature data for crambine B,[5] except that the side chain has eleven carbons in the synthetic sample rather than nine carbons as in the major congener of the natural product. The synthetic material is one of the minor congeners of the natural product.

**7-[(Aminoiminomethyl)amino]heptyl 2-amino-1,4-dihydro-6-(3-hydroxypropyl)-4-undecylpyrimidine-5-carboxylate hydrochloride (9d, crambine C1)** was prepared in 88% yield from **40d** by hydrogenolysis as described above for crambine A and in 94% yield by stirring a solution of crambine B (**45d**) (5 mg) in MeOH–$H_2O$ (1:1, 3 mL) with $Na_2CO_3$ (2 mg) at rt for 12 h. One drop of HCl was added and the solution was concentrated under reduced pressure. The residue was taken up in 7:3 $CH_2Cl_2$–MeOH filtered to remove NaCl and concentrated to afford pure **9d**: $^1$H NMR ($CD_3OD$) 4.41 (dd, 1, $J$ = 5.0, 6.7), 4.18 (m, 2), 3.61 (t, 2, $J$ = 6.4), 3.17 (2, t, $J$ = 7.0), 2.82 (m, 2), 1.81 (m, 2), 1.69 (m, 2), 1.58 (m, 4) 1.2–1.5 (m, 24) 0.90 (t, 3, $J$ = 6.7); $^{13}$C NMR ($CD_3OD$) 166.3, 159.0, 153.7, 149.1, 106.3, 66.1, 62.4, 51.4, 42.8, 37.3, 33.4, 32.3, 31.1, 31.1, 31.0, 30.9, 30.8, 30.6, 30.2, 30.1, 29.9, 29.0, 27.9, 27.4, 25.4, 24.0, 14.7; IR (neat) 3000–3500, 2924, 2854, 1692, 1620, 1558, 1465, 1392, 1355, 1248, 1090.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1$H, $J$, $^{13}$C) C-1 (159.0), $H_2C$-2 (3.17 t, 7.0; 42.8), $H_2C$-3 (1.58 m; 30.1), $H_2C$-3A (1.20–1.50 m; 27.4), $H_2C$-3B (1.20–1.50 m; 29.9), $H_2C$-3C (1.20–1.50 m; 27.9), $H_2C$-4 (1.69 m; 30.2), $H_2C$-5 (4.18 m; 66.1), C-6 (166.3), C-7 (106.3), C-8 (149.1), $H_2C$-9 (2.82 m; 29.0), $H_2C$-10 (1.81 m; 32.3), $H_2C$-11 (3.61 t, 6.4; 62.4), C-12 (153.7), HC-13 (4.41 dd, 5.0/6.7; 51.4), $H_2C$-14 (1.58 m; 37.3), $H_2C$-15 (1.20–1.50 m; 25.4), $H_2C$-16 to $H_2C$-21 (1.20–

1.50 m; 31.1, 31.1, 31.0, 30.9, 30.8, 30.6), $H_2C$-22 (1.20–1.50 m; 33.4), $H_2C$-23 (1.20–1.50 m; 24.0), $H_2C$-24 (0.90 t, 6.7; 14.7). The $^{13}C$ NMR shift for $H_2C$-10 differs from the literature data,[6] but is identical to that of **9a**, **39b**, **40b**, **39c**, and **40c**. All other data are identical to the literature data.[6]

**4-[(Aminoiminomethyl)amino]butyl 2-amino-4-undecyl-1,4-dihydro-6-(3-hydroxypropyl)pyrimidine-5-carboxylate hydrochloride (9a, crambine C2)** was prepared in 91% yield from **40a** by hydrogenolysis as described above for crambine A: $^1H$ NMR ($CD_3OD$) 4.43 (t, 1, $J$ = 5.5), 4.22 (m, 2), 3.62 (t, 2, $J$ = 6.1), 3.23 (t, 2, $J$ = 6.8), 2.82 (m, 2), 1.80 (m, 4), 1.70 (m, 2), 1.58 (m, 2), 1.20–1.40 (m, 18), 0.90 (t, 3, $J$ = 6.7); $^{13}C$ NMR ($CD_3OD$) 166.3, 158.9, 153.7, 149.3, 106.2, 65.6, 62.4, 51.4, 42.4, 37.3, 33.4, 32.3, 31.05, 31.05, 30.96, 30.93, 30.77, 30.64, 29.1, 27.3, 27.0, 25.4, 24.0, 14.7; IR (neat) 3000–3450, 2924, 2853, 1658, 1610, 1549, 1534, 1466, 1384, 1264, 1061.

The NMR ($CD_3OD$) spectral data by carbon number using the numbering from ref 5: ($^1H$, $J$, $^{13}C$) C-1 (158.9), $H_2C$-2 (3.23 t, 6.8; 42.4), $H_2C$-3 (1.70 m; 27.0), $H_2C$-4 (1.80 m; 27.3), $H_2C$-5 (4.22 m; 65.6), C-6 (166.3), C-7 (106.2), C-8 (149.3), $H_2C$-9 (2.82 m; 29.1), $H_2C$-10 (1.81 m; 32.3), $H_2C$-11 (3.62 t, 6.1; 62.4), C-12 (153.7), HC-13 (4.43 t, 5.5; 51.4), $H_2C$-14 (1.58 m; 37.3), $H_2C$-15 (1.20–1.40 m; 25.4), $H_2C$-16 to $H_2C$-21 (1.20–1.40 m; 31.05, 31.05, 30.96, 30.93, 30.77, 30.64), $H_2C$-22 (1.20–1.40 m; 33.4), $H_2C$-23 (1.20–1.40 m; 24.0), $H_2C$-24 (0.90 t, 6.7; 14.7). The $^1H$ NMR data are identical to the literature data.[6]

**Acknowledgment.** We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. We thank Prof. Thomas Pochapsky, Mr. Anping Wang, and Ms. Sophie Kazanis for carrying out the ROESY experiments. We thank Prof. Braekman for spectral data of crambines A and B and for an authentic sample of crambine B. We thank Prof. Rinehart and Dr. Jares-Erijman for the biological activity data, mass spectral data of **45a–d**, and many helpful discussions.

**Supplementary Material Available:** Experimental procedures and spectral data for all compounds not described in the experimental section (16 pages). This material is contained in libraries of microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.