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Synthesis of a Structural Analog of Ptilomycalin A

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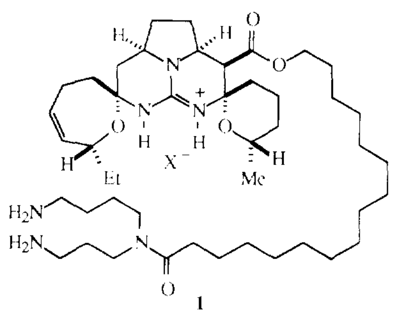
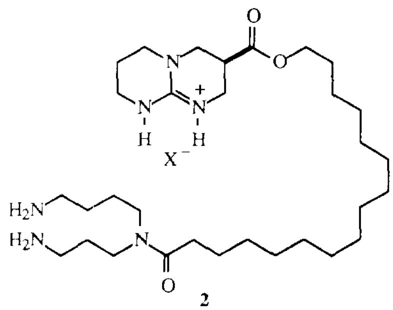
Abstract: Ptilomycalin A analog **2** was prepared by coupling amido alcohol **9** with guanidinium carboxylate **31**. The synthesis of **2** requires 13 steps via a longest linear sequence from acrylate **22**.

Introduction. Ptilomycalin A (**1**) is a polycyclic marine alkaloid which was isolated in 1989 from the Caribbean sponge *Ptilocaulis spiculifer* and also from a red *Hemimycale* sponge of the Red Sea.[1] Ptilomycalin A exhibits antitumor, antiviral, and antifungal activity at low concentrations. Because of its biological activity and interesting structure, ptilomycalin A has been the focus of recent synthetic efforts.[2] For example, Snider has reported a biomimetic synthesis of the guanidinium nucleus of ptilomycalin A and Overman recently reported a total synthesis of the natural product.[3,4,5] We report here a synthesis of compound **2**, a simple structural analog of **1** which contains a bicyclic guanidine attached via an ester linkage to the amido alcohol portion of ptilomycalin A.[6,7]



1

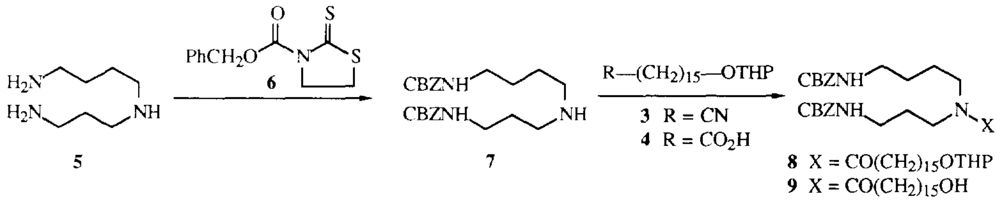


2

Preparation of Amido Alcohol 9. We first prepared the amido alcohol portion of **2** by coupling 16-hydroxyhexadecanoic acid derivative **4** with protected spermidine derivative **7** as shown in Scheme 1. Thus, nitrile **3** was prepared in four steps from propargyl alcohol according to literature procedures.[8] Subsequent heating of **3** in 10 M sodium hydroxide and methanol afforded carboxylic acid **4** in 95% yield. Selective protection of the two primary amino groups in spermidine (**5**) was accomplished upon treatment with two equivalents of 1-acylthiazolidine-2-thione **6** to give carbamate **7** in 52% yield.[9] The coupling of carboxylic acid **4** with amine **7** was initially accomplished using dicyclohexylcarbodiimide in the presence of a catalytic amount of 4-dimethylaminopyridine.[10] However, the yield of amide **8** was only 57%. When 1-hydroxybenzotriazole was substituted for the 4-

dimethylaminopyridine, however, amide **8** was obtained in 95% yield.[11] Hydrolysis of the tetrahydropyranyl ether was accomplished using acidic Dowex-50 in methanol to give **9** in 80% yield.[12]

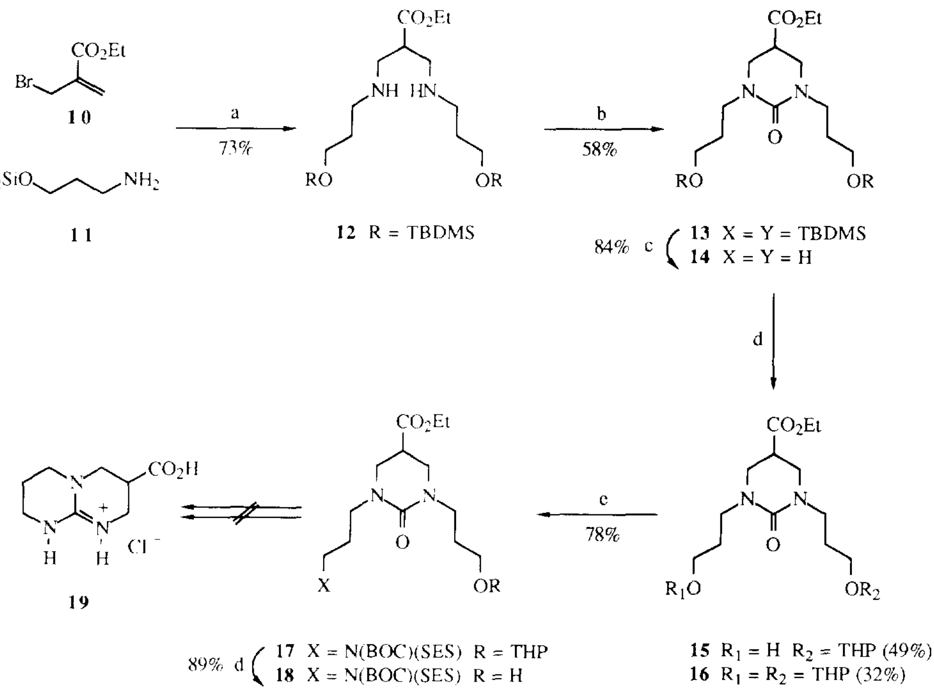
Scheme 1



Preparation of Carboxylic Acid 19. We next prepared the carboxylic acid portion of **2**. Many syntheses of bicyclic guanidines have been described.[12] A number of these revolve around construction of cyclic ureas or thioureas and thus, it was decided to initially approach **19** from a symmetrical urea such as **13**. One nitrogen substituent was to serve as a handle for introducing the second ring of the bicyclic guanidine and the other was ultimately to be converted to a hydrogen. Ethyl 2-bromomethylacrylate (**10**) was to serve as a point of departure.[13] In the event, treatment of **10** with three equivalents of primary amine **11** gave the double addition product **12** in 73% yield.[14] Conversion of **12** to cyclic urea **13** was then accomplished in 58% yield using carbonyldiimidazole.[15] Deprotection of **13** was straightforward and provided diol **14** in 84% yield. Unfortunately, use of diol **14** as an intermediate in the synthesis of **2** was fraught with difficulties. For example, it was possible to convert **14** into tetrahydropyranyl ether **15** in 49% yield, accompanied not unexpectedly by the diprotected compound **16** (35%) and starting material (8%). It was also possible to convert **15** into protected amines **17** (78%) and **18** (89%).[16] But a number of procedures for removing the 3-hydroxypropyl group from **18** met with failure.[17] In addition, attempts to convert ureas of type **18** to the corresponding thioureas, with the hope of using such intermediates as handles for constructing the bicyclic guanidine, were also problematic.

Due to these desymmetrization and deprotection problems, a variant of this strategy that did not rely on the use of symmetrical intermediates was adopted. Acrylate **10** once again served as the starting point. Treatment of this material with dibenzylamine and potassium carbonate in acetonitrile gave allylic amine **20** in 98% yield.[18] This amine, however, failed to react with amine **11** and provided a mixture of products resulting from 1,4-addition and 1,2-addition when treated with the corresponding lithium amide **21**. With the hope that a more hindered ester would suppress 1,2-addition, *tert*-butyl 2-bromomethylacrylate (**22**) became the point of departure (Scheme 3).[19] This acrylate reacted smoothly with dibenzylamine to afford **23** (82%) and treatment of this unsaturated ester with lithium amide **21** gave diamine **24** in 66% yield.[20] Protection of the nitrogen gave carbamate **25** (84%)[9] and removal of the silicon protecting group gave alcohol **26** (97%).[21] Displacement of the alcohol using ammonia equivalent **27** under Mitsunobu conditions provided sulfonamide **28** in 94% yield.[22] Hydrogenolysis removed the two carbobenzoxy protecting groups and the two benzyl groups and the resulting crude diamine was treated with thiocarbonyldiimidazole to afford cyclic thiourea **29** in 51% yield. Alkylation of **29** using iodomethane, followed by treatment of the intermediate thioimidate salt with Hunig's base gave bicyclic guanidine **30** in 81% yield.[23] Treatment of **30** with hydrogen chloride in dichloromethane provided guanidinium salt **31** (93%) and tetra-*n*-butylammonium fluoride mediated removal of the SES group gave a quantitative yield of guanidinium salt **19**.[24]

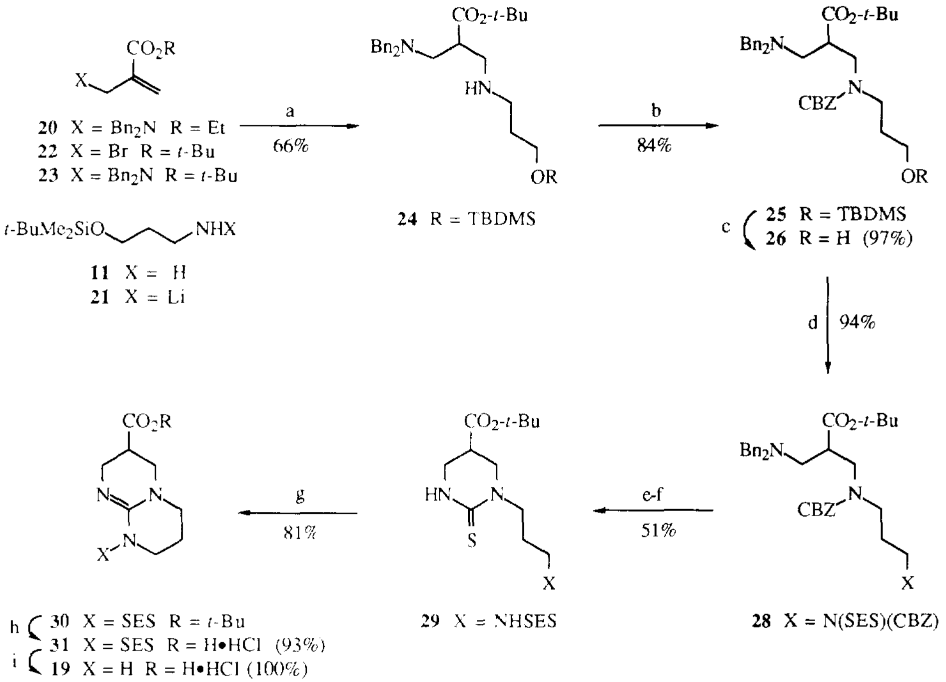
Scheme 2



(a) $CHCl_3$, rt (b) $(Im)_2C{=}O$, PhH, Δ (c) Dowex-50 (H^+), MeOH, rt (d) DHP (1.2 equiv), PPTS, CH_2Cl_2, rt (e) $HN(SO_2CH_2CH_2SiMe_3)(CO_2\text{-}t\text{-}Bu)$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, rt

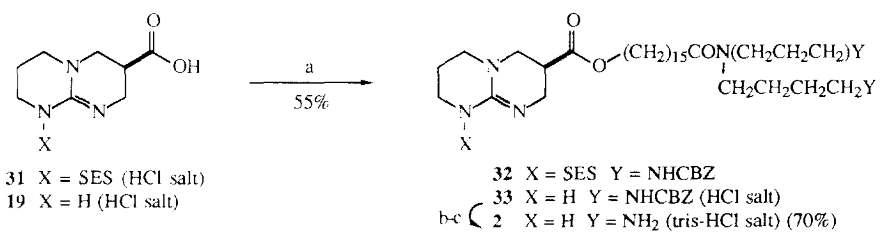
Preparation of Ptilomycalin A Analog 2. The preparation of analog **2** is described in Scheme 4. Treatment of guanidinium salt **31** and alcohol **9** with dicyclohexylcarbodiimide and 4-dimethylaminopyridine in dimethylformamide (DMF) gave ester **32** in 65% yield.[10] Attempts to remove the SES protecting group using tetra-*n*-butylammonium fluoride or cesium fluoride, however, were accompanied by ester hydrolysis. Coupling of guanidinium salt **19** with alcohol **9** could be accomplished using 3-[(dimethylamino)propyl]ethylcarbodiimide hydrochloride and 4-dimethylamino-pyridine in DMF to afford **33** in 55% yield.[25] Finally, removal of the CBZ protecting groups by hydrogenolysis and treatment of the resulting diamine with hydrochloric acid gave **2** as the tris-hydrochloride salt.[26] It is notable that while carbamate **33** had excellent shelf-life, neat amine **2** underwent an unidentified process over a period of a few weeks that led to cleavage of the ester linkage, thus precluding its biological evaluation.[27]

Scheme 3



(a) **21** + **23**, THF, -78°C (b) $PhCH_2OCOCl$, Et_3N, THF, 0°C (c) Bu_4NF, THF, rt (d) Ph_3P, $EtO_2CN{=}NCO_2Et$, $HN(SO_2CH_2CH_2SiMe_3)(OCOCH_2Ph)$ (**27**), THF, rt (e) $Pd(OH)_2$, H_2, EtOH (f) $(Im)_2C{=}S$, CH_2Cl_2, Δ (g) MeOH, CH_3I, Δ (h) HCl, CH_2Cl_2 (i) Bu_4NF, DMF; HCl, H_2O

Scheme 4



(a) **19** + **9**, DMF, $Et_2NCH_2CH_2CH_2N{=}C{=}NCH_2CH_3{\bullet}HCl$, 4-DMAP (b) $Pd(OH)_2$, 1,4-cyclohexadiene, EtOH (c) HCl, MeOH

In summary, ptilomycalin A analog **2** was prepared by coupling amido alcohol **9** with guanidinium carboxylate **19**. The synthesis of **2** describes the first synthesis of octahydro-9aH-pyrimido[1,2-a]pyrimidine-3-carboxylates, requires 13 steps via a longest linear sequence from acrylate **22** and proceeds in 6% overall yield.

Experimental Section

All melting and boiling points are uncorrected. ^1H NMR spectra were recorded using 200-500 MHz instruments and are recorded as follows: Chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants in Hz, integration, interpretation]. Interpretations were aided in certain cases by decoupling experiments. ^{13}C NMR spectra are reported as follows: chemical shift (multiplicity from DEPT spectra). Mass spectra were obained at an ionization potential of 70 ev unless stated otherwise. Solvents and reagents were dried and purified prior to use as necessary. Reactions requiring an inert atmosphere were run under a blanket of argon. Column chromatography was normally performed using flash chromatography conditions over silica gel. Reagents were purchased from commercial suppliers unless otherwise specified.

16-[(Tetrahydro-2H-pyran-2-yl)oxy]hexadecanoic acid (4). To a solution of 1.12 g (3.32 mmol) of nitrile **3**[8] in 66 mL of methanol was added 56 mL of 10 M aqueous sodium hydroxide. The mixture was heated at reflux for 28 h, cooled in an ice bath, acidified to pH 2 with concentrated hydrochloric acid and the resulting solution was extracted with four 100-mL portions of ether. The combined organic extracts were washed with two 100-mL portions of water, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography over silica gel (eluted with chloroform-methanol, 95:5) to afford 1.15 g (97%) of carboxylic acid **4** as a white solid: mp 50-52°C; IR ($CHCl_3$) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 28H, CH_2), 1.53-1.82 (m, 4H, CH_2), 2.34 (t, J = 7.4 Hz, 2H, CH_2CO), 3.32-3.43 (m, 1H, CH_2O), 3.45-3.56 (m, 1H, CH_2O), 3.67-3.79 (m, 1H, CH_2O), 3.82-3.93 (m, 1H, CH_2O), 4.57 (m, 1H, OCHO); the acidic proton was not seen; ^{13}C NMR ($CDCl_3$) δ 19.7 (t), 24.7 (t), 25.5 (t), 26.2 (t), 29.1 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 30.8 (t), 34.0 (t), 62.3 (t), 67.7 (t), 98.8 (d), 179.2 (s); exact mass calcd. for $C_{21}H_{40}O_4$ *m/e* 356.2927, found *m/e* 356.2890. Anal. calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. found C, 70.78, H, 11.32.

[3-[[4-(Carboxyamino)butyl]amino]propyl]carbamic acid, dibenzyl ester (7). To a solution of 2.42 g (16.6 mmol) of spermidine **5** in 70 mL of dichloromethane stirred at room temperature was added dropwise over 1.5 h a solution of 7.00 g (27.6 mmol) of 3-(carboxybenzyl)-thiazolidine-2-thione (**6**)[9] in 28 mL of dichloromethane. The mixture was stirred at room temperature for 1.5 h and concentrated in vacuo to afford a white solid. The apolar thiazolidine-2-thione was removed by filtration through a short pad of silica gel (eluted with dichloromethane-methanol, 10:1) to yield a white solid which was recrystallized from ethyl acetate-hexanes to afford 2.84 g (52%) of amine **7** as a white solid: mp 103-105°C; IR ($CHCl_3$) 3451, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48-1.60 (m, 5H, CH_2, NH), 1.62-1.72 (m, 2H, CH_2), 2.58 (t, J = 6.5 Hz, 2H, CH_2NH), 2.66 (t, J = 7.0 Hz, CH_2N), 3.12-3.20 (m, 2H, CH_2NCO), 3.24-3.32 (m, 2H, CH_2NCO), 5.08 (s, 4H, CH_2O), 5.18 (br s, 1H, NH), 5.51 (br s, 1H, NH), 7.32-7.42 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.3 (t), 27.7 (t), 29.5 (t), 39.8 (t), 40.9 (t), 47.6 (t), 49.3 (t), 66.4 (t), 128.0 (d), 128.3 (d), 128.4 (d), 136.7 (s), 136.8 (s), 156.5 (s); Anal. calcd. for $C_{23}H_{31}N_3O_4$: C, 66.80; H, 7.56. found C, 66.75; H, 7.61.

[3-[*N*-[4-(Carboxyamino)butyl]-16-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexadecanamide]propyl]carbamic acid, dibenzyl ester (8). To a solution of 1.07 g (3.0 mmol) of carboxylic acid **4** and 1.24 g (3.0 mmol) of amine **7** in 54 mL of tetrahydrofuran was added 0.618 g (3.0 mmol) of dicyclohexylcarbodiimide and 42 mg (0.3 mmol) of 1-hydroxybenzotriazole. The reaction mixture was stirred at room temperature for 27 h, filtered and concentrated in vacuo. The residue was purified by column chromatography over 50 g of silica gel (eluted with 600 mL of ethyl acetate-hexanes, 1:1 then 700 mL of ethyl acetate-hexanes, 2:1) to afford 2.17 g (95%) of amide **8** as a colorless oil: IR (neat) 3327, 1721, 1628 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 1.29 (s, 23H, CH_2), 1.48-1.54 (m, 11H, CH_2), 1.65-1.74 (m, 4H, CH_2) 2.25 (t, J = 7.2 Hz, 2H, CH_2CO), 3.01-3.10 (m, 4H, CH_2N), 3.22-3.31 (m, 4H, CH_2NH), 3.34-3.47 (m, 2H, CH_2O), 3.59-3.68 (m, 1H, CH_2O), 3.75-3.82 (m, 1H, CH_2O), 4.55 (m, 1H, OCHO), 5.06 (s, 4H, CH_2Ph), 6.80 (br s, 2H, NH), 7.30-7.37 (s, 10H, Ph); ^{13}C NMR (DMSO-d_6 at 373K) δ 18.7 (t), 24.4 (t), 25.1 (t), 26.4 (t), 28.2 (t), 28.27 (t), 28.31 (t), 28.7 (t), 29.9 (t), 31.7 (t), 37.8 (t), 60.9 (t), 64.68 (t), 64.74 (t), 66.2 (t), 97.6 (d), 126.9 (d), 127.0 (d), 127.6 (d), 136.8 (s), 155.5 (s), 171.3 (s); mass spectrum (FAB) *m/e* (relative intensity) 751.7 (M^+, 1.99), 668.5 (100).

[3-[*N*-[4-(Carboxyamino)butyl]-16-hydroxyhexadecanamide]propyl]carbamic acid, dibenzyl ester (9). To a solution of 1.90 g (2.85 mmol) of amide **8** in 40 mL of methanol was added 400 mg of acidic Dowex-50 resin. The mixture was stirred at room temperature for 8 h and filtered. The filtrate was concentrated in vacuo to afford a white solid. Recrystallization from ethyl acetate-hexanes afforded 1.46 g (87%) of alcohol **9** as a white solid: mp 75-76.5°C; IR ($CHCl_3$) 3684, 3624, 3452, 1715, 1625 cm^{-1}; ^1H NMR (DMSO-d_6 at 363K) δ 1.28 (s, 20H, CH_2), 1.43-1.53 (m, 10H, CH_2), 1.65-1.70 (m, 2H, CH_2), 2.25 (t, J = 7.2 Hz, 2H, CH_2CO), 3.03-3.10 (m, 5H, NCH_2 and OH), 3.22-3.30 (m, 4H, NCH_2), 3.43 (t, J = 6.3 Hz, 2H, CH_2O), 5.06 (s, 4H, CH_2Ph), 6.86 (br s, 2H, NH), 7.31-7.37 (m, 10H, Ph); ^{13}C NMR (DMSO-d_6 at 373K) δ 24.5 (t), 24.9 (t), 26.4 (t), 28.2 (t), 28.3 (t), 31.7 (t), 32.0 (t), 37.8 (t), 60.4 (t), 64.7 (t), 64.8 (t), 126.9 (d), 127.0 (d), 127.6 (d), 128.9 (d), 136.8 (s), 136.9 (s), 153.9 (s), 155.5 (s), 171.3 (s); mass spectrum (FAB) *m/e* (relative intensity) 668.5 (M^++1, 100). Anal. calcd. for $C_{39}H_{61}N_3O_6$: C, 70.13; H, 9.21. found C, 69.53; H, 9.16.

3-(*tert*-Butyldimethylsiloxy)-1-propylamine (11). To a solution of 5.63 g (75.0 mmol) of 3-amino-1-propanol in 300 mL of benzene chilled in a water bath at 10°C was added 24.8 mL (165 mmol) of diazabicyclo[2.2.2]undecene and 23.74 g (157.5 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was heated at reflux for 1.5 h, allowed to cool to room temperature and filtered. The filtrate was concentrated in vacuo to afford 23.95 g of a yellow oil which was diluted with 135 mL of methanol. The solution was chilled in an ice bath and 2.1 g of acidic Dowex-50 resin was added. The mixture was stirred at 0°C for 15 min, filtered and was concentrated in vacuo. The crude oil was purified by distillation under reduced pressure to afford 11.96 g (92%) of amine **11** as a colorless oil: bp 64-66°C (3.5 mm); IR (neat) 3373 cm^{-1}: ^1H NMR ($CDCl_3$) δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $C(CH_3)_3$), 1.45 (br s, 2H, NH_2), 1.60 (p, J = 6.4 Hz, 2H, CH_2), 2.74 (t, J = 6.7 Hz, 2H, CH_2N), 3.64 (t,J = 6.1 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ -5.4 (q), 18.2 (s), 25.9 (q), 36.4 (t), 39.4 (t), 61.2 (t); exact mass calcd. for $C_9H_{23}NOSi$ *m/e* 189.1549, found *m/e* 189.1556.

***N*-[3-(*tert*-Butyldimethylsiloxy)propyl]-2-[[3-(*tert*-butyldimethylsiloxy)propylamino]methyl]-β-alanine, ethyl ester (12).** To a solution of 21.7 g (125 mmol) of amine **11** in 75 mL of chloroform chilled in an ice bath was added dropwise over 3 h a solution of 8.04 g (41.7 mmol) of ethyl 2-(bromomethyl)acrylate (**10**)[13] in 120 mL of chloroform. The mixture was allowed to warm up to room temperature over 1 h, heated at reflux for 19 h, cooled to room temperature and washed with 400 mL of 1 M aqueous sodium hydroxide. The aqueous wash was extracted with three 400-mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by column chromatography over 250 g of silica gel (eluted with dichloromethane-methanol, 25:1) to afford 14.99 g (73%) of diamine **12** as a pale yellow oil: IR (neat) 3354, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 12H, $Si(CH_3)_2$), 0.87 (s, 18H, $C(CH_3)_3$), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.59-1.72 (m, 6H, CH_2 and NH), 2.62-2.90 (m, 9H, CH_2N and CHCO), 3.64 (t,J = 6.2 Hz, 4H, CH_2OSi), 4.14 (q, J = 7.1 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ -5.4 (q), 14.2 (q), 18.3 (s), 25.9 (q), 32.4 (t), 44.8 (d), 46.8 (t), 50.2 (t), 60.7 (t), 61.3 (t), 173.7 (s); exact mass calcd. for $C_{24}H_{54}N_2O_4Si_2$ *m/e* 490.3622, found *m/e* 490.3623.

Ethyl hexahydro-1,3-[3-(*tert*-butyldimethylsiloxy)propyl]-2-oxo-5-pyrimidinecarboxylate (13). A solution of 8.83 g (18.0 mmol) of diamine **12** and 4.37 g (27.0 mmol) of carbonyldiimidazole in 70 mL of benzene was heated at reflux for 17 h and concentrated in vacuo. The crude oil was purified by column chromatography over 90 g of silica gel (eluted with 1.1 L of ethyl acetate-hexanes, 1:4 then with 400 mL of ethyl acetate-hexanes, 1:3) to afford 5.35 g (58%) of urea **13** as a pale yellow oil: IR (neat) 1738, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 12H, $Si(CH_3)_2$), 0.88 (s, 18H, $C(CH_3)_3$), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.75 (p, J = 6.8 Hz, 4H, CH_2), 2.87-3.00 (m, 1H, CHCO), 3.25-3.57 (m, 8H, CH_2N), 3.63 (t,J = 6.3 Hz, 4H, CH_2OSi), 4.17 (q, J = 7.1 Hz, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ -5.4 (q), 14.1 (q), 18.3 (s), 25.9 (q), 31.1 (t), 38.4 (d), 45.5 (t), 47.4 (t), 60.9 (t), 61.2 (t), 155.3 (s), 173.7 (s); exact mass calcd. for $C_{25}H_{52}N_2O_5Si_2$ *m/e* 516.3415, found *m/e* 516.3419.

Ethyl hexahydro-1,3-(3-hydroxypropyl)-2-oxo-5-pyrimidinecarboxylate (14). A solution of 5.74 g (11.1 mmol) of urea **13** and 0.80 g of strongly acidic Dowex resin in 170 mL of methanol was stirred at room temperature for 4.5 h, filtered and concentrated in vacuo. The crude oil was purified by column chromatography over silica gel (eluted with dichloromethane-methanol, 10:1), to yield 2.69 g (84%) of diol **14** as a pale yellow oil: IR (neat) 3386, 1733, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.63-1.73 (m, 4H, CH_2), 2.92-2.99 (m, 1H, CHCO), 3.34-3.54 (m, 12H, CH_2N and CH_2O), 3.87 (t,J = 7.0 Hz, 2H, OH), 4.19 (q, J = 7.1 Hz, 2H, CH_2OCO); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 29.8 (t), 37.9 (d), 44.2 (t), 46.6 (t), 58.0 (t), 61.6 (t), 157.2 (s), 170.3 (s); exact mass calcd. for $C_{13}H_{24}N_2O_5$ *m/e* 288.1685, found *m/e* 288.1691.

Ethyl hexahydro-1,3-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-2-oxo-5-pyrimidinecarboxylate (16) and ethyl hexahydro-1-(3-hydroxypropyl)-3-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-2-oxo-5-pyrimidinecarboxylate (15). To a solution of 2.60 g (9.01 mmol) of diol **14** in 65 mL of dichloromethane was added 0.91 g (1.02 mL, 10.8 mmol) of 3,4-dihydro-2*H*-pyran and 0.23 g (0.901 mmol) of pyridinium *p*-toluenesulfonate. The solution was stirred at room temperature for 22 h, diluted with 150 mL of dichloromethane and washed with 200 mL of halfsaturated brine. The aqueous wash was extracted with two 150-mL portions of dichloromethane and 150 mL of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (eluted with dichloromethane-methanol, 35:1) to yield 484 mg (35%) of diprotected urea **16** as an oil: IR (neat) 1735, 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.44-1.62 (m, 8H, CH_2), 1.64-1.74 (m, 2H, CH_2), 1.74-1.86 (m, 6H, CH_2), 2.88-2.97 (m, 1H, CHCO), 3.29-3.53 (m, 12H, CH_2N and CH_2O), 3.70-3.86 (m, 4H, CH_2O), 4.15 (q, J = 7.1 Hz, 2H, CH_2OCO), 4.53 (m, 2H, OCHO); ^{13}C NMR ($CDCl_3$,) δ 14.1 (q), 19.58 (t)*, 19.63 (t)*, 25.4 (t), 28.1 (t), 30.7 (t), 38.3 (d), 45.7 (t), 47.2 (t), 61.2 (t), 62.28 (t)*, 62.34 (t)*, 65.23 (t)*, 65.28 (t)*, 98.9 (d), 155.2 (s), 170.7 (s); exact mass calcd. for $C_{21}H_{35}N_2O_6$ (M-OEt) *m/e* 411.2497, found *m/e* 411.2568 and for $C_{18}H_{31}N_2O_5$ (M^+–OTHP) *m/e* 355.2234, found *m/e* 355.2299. Further elution afforded 1.642 g (49%) of alcohol **15** as an oil: IR (neat) 3381, 1735, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.45-1.59 (m, 4H, CH_2), 1.60-1.74 (m, 3H, CH_2), 1.75-1.85 (m, 3H, CH_2); 2.89-2.97 (m, 1H, CHCO), 3.31-3.64 (m, 12H, CH_2N and CH_2O), 3.70-3.86 (m, 2H, CH_2O), 4.16 (q, J = 7.1 Hz, 2H, CH_2OCO), 4.39 (t, J = 6.9 Hz, 1H, OH), 4.53 (m, 1H, OCHO); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.6 (t), 25.4 (t), 27.98 (t)*, 28.01 (t)*, 29.6 (t), 30.6 (t), 38.0 (d), 43.7 (t), 45.9 (t), 46.6 (t), 47.05 (t)*, 47.08 (t)*, 57.8 (t), 61.3 (t), 62.38 (t)*, 62.41 (t)*, 65.03 (t)*, 65.09 (t)*, 99.0 (d), 156.3 (s), 170.5 (s); exact mass calcd. for $C_{18}H_{32}N_2O_5$ (M^+–OH) *m/e* 355.2234, found *m/e* 355.2251. Further elution afforded 195 mg (8%) of starting material.

1-[3-[*N*-Carboxy-2-(trimethylsilyl)ethanesulfonamido]propyl]-3-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]hexahydro-2-oxo-5-pyrimidinecarboxylic acid, *N*-*tert*-butyl ethyl ester (17). To a solution of 1.01 g (2.71 mmol) of alcohol **15** in 80 mL of tetrahydrofuran chilled in an ice bath was added successively 1.52 g (5.42 mmol) of *tert*-butyl [[2-(trimethylsilyl)ethyl]-sulfonyl]carbamate,[24] 2.13 g (8.12 mmol) of triphenylphosphine and 1.03 mL (6.50 mmol) of diethyl azodicarboxylate dropwise over 5 min. The orange solution was stirred at 0°C for 5 min, at room temperature for 1 h and concentrated in vacuo. The semi-solid residue was purified by column chromatography over 50 g of silica gel (eluted with ethyl acetate-hexanes, 3:2 then 2:1) to yield 1.34 g of sulfonamide **17** as a pale yellow oil: IR (neat) 1728, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9H, $Si(CH_3)_3$), 0.89-0.95 (m, 2H, CH_2Si), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 1.39-1.53 (m, 4H, CH_2), 1.62-1.73 (m, 1H, CH_2), 1.75-1.91 (m, 5H, CH_2), 2.89-2.98 (m, 1H, CHCO), 3.25-3.53 (m, 12H, CH_2N, CH_2O and CH_2SO_2), 3.60-3.65 (m, 2H, CH_2NSO_2), 3.69-3.84 (m, 2H, CH_2O), 4.15 (q, J = 7.1 Hz, 2H, CH_2OCO), 4.52 (m, 1H, OCHO); ^{13}C NMR ($CDCl_3$) δ -2.1 (q), 10.3 (t), 14.1 (q), 19.58 (t)*, 19.62 (t)*, 25.4 (t), 27.9 (q), 28.1 (t), 28.6 (t), 30.7 (t), 38.2 (d), 44.9 (t), 45.3 (t), 45.8 (t), 46.7 (t), 47.2 (t), 50.7 (t), 61.2 (t), 62.26 (t)*, 62.32 (t)*, 65.19 (t)*, 65.24 (t)*, 84.1 (s), 98.9 (d), 151.6 (s), 155.3 (s), 170.6 (s); exact mass calcd. for $C_{28}H_{53}N_3O_9SSi$ *m/e* 635.3274, found *m/e* 635.3247.

1-[3-[*N*-Carboxy-2-(trimethylsilyl)ethanesulfonamido]propyl]-3-(3-hydroxypropyl)hexahydro-2-oxo-5-pyrimidinecarboxylic acid, *N*-*tert*-butyl ethyl ester (18). To a solution of 1.26 g (1.98 mmol), of tetrahydropyranyl ether **17** in 30 mL of methanol was added 125 mg of acidic Dowex-50 resin. The mixture was stirred at room temperature for 20 h, filtered and concentrated in vacuo. The residue was purified by column chromatography over 50 g of silica gel (eluted with 700 mL of ethyl acetate-hexanes, 5:2 then 600 mL of ethyl acetate-hexanes, 3:1) to yield 0.970 g (89%) of alcohol **18** as a pale yellow oil: IR (neat) 3386, 1728, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, $Si(CH_3)_3$), 0.90-0.97 (m, 2H, CH_2Si), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$), 1.60-1.68 (m, 2H, CH_2), 1.83-1.93 (m, 2H, CH_2), 2.92-3.00 (m, 1H, CHCO), 3.24-3.55 (m, 12H, CH_2N, CH_2O and CH_2SO_2), 3.57-3.65 (m, 2H, CH_2NSO_2), 4.16 (q, J = 7.1 Hz, 2H, CH_2OCO), 4.34 (t, J = 6.6 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ -2.1 (q), 10.2 (t), 14.0 (q), 27.9 (q), 28.6 (t), 29.6 (t), 37.8 (d), 43.7 (t), 44.7 (t), 45.5 (t), 46.6 (t), 50.7 (t), 57.7 (t), 61.3 (t), 84.2 (s), 151.5 (s), 156.4 (s), 170.4 (s); one carbon was not observed; exact mass calcd. for $C_{23}H_{45}N_3O_8SSi$ *m/e* 551.2699, found *m/e* 551.2713.

Ethyl [2-(dibenzylamino)methyl]acrylate (20). To a solution of 0.386 g (2.0 mmol) of ethyl 2-(bromomethyl)acrylate (**10**)[13] in 3 mL of acetonitrile was added 0.332 g (2.4 mmol) of potassium carbonate and 0.395 g (2.2 mmol) of dibenzylamine in 1 mL of acetonitrile. The mixture was stirred at room temperature for 10 min, at 65°C for 3 h, cooled and partitioned between 20 mL of water and 20 mL of dichloromethane. The aqueous layer was extracted with two 20-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over 10 g of silica gel (eluted with hexanes-ethyl acetate, 10:1) to afford 0.618 g (98%) of ester **20** as a pale yellow oil: IR (neat) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H, CH_3), 3.33 (t, J = 1.3 Hz, 2H, CH_2C=), 3.61 (s, 4H, CH_2N), 4.20 (q, J = 7.1 Hz, 2H, CH_2O), 6.00 (d, J = 1.7 Hz, 1H, =CH_2), 6.29 (d, J = 1.7 Hz, 1H, =CH_2), 7.20-7.40 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 53.9 (t), 58.1 (t), 60.6 (t), 125.7 (t), 126.9 (d), 128.2 (d), 128.5 (d), 138.5 (s), 139.4 (s), 167.0 (s); exact mass calcd. for $C_{20}H_{23}NO_2$ *m/e* 309.1729, found *m/e* 309.1702.

***tert*-Butyl 2-[(dibenzylamino)methyl]acrylate (23).** To a solution of 13.15 g (59.6 mmol) of *tert*-butyl 2-(bromomethyl)acrylate (**22**)[19] and 9.91 g (71.5 mmol) of potassium carbonate in 89 mL of acetonitrile was added dropwise over 15 min a solution of 11.6 mL (65.6 mmol) of dibenzylamine in 31 mL of acetonitrile. The mixture was heated at reflux for 3h and partitioned between 400 mL of water and 400 mL of dichloromethane. The aqueous layer was extracted with two 350-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The yellow solid residue was recrystallized from boiling hexanes to yield 16.37 g (82%) of ester **23** as a white solid: mp 52-54°C; IR ($CHCl_3$) 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H, $C(CH_3)_3$), 3.28 (s, 2H, CH_2C=), 3.59 (s, 4H, CH_2N), 5.95 (d, J = 1.8 Hz, 1H, =CH_2), 6.19 (d, J = 1.8 Hz, 1H, =CH_2), 7.23-7.41 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 28.1 (q), 54.0 (t), 58.0 (t), 80.6 (s), 124.7 (t), 126.8 (d), 128.2 (d), 128.6 (d), 139.5 (s), 139.8 (s), 166.4 (s); exact mass calcd. for $C_{22}H_{27}NO_2$ *m/e* 337.2042, found *m/e* 337.2012.

***N*,*N*-Dibenzyl-2-[[3-(*tert*-butyldimethylsiloxy)propylamino]methyl]-β-alanine, *tert*-butyl ester (24).** To a solution of 10.56 g (55.9 mmol) of amine **11** in 250 mL of tetrahydrofuran stirred at -78°C was added 36.4 mL (58.3 mmol) of *n*-butyllithium (1.6 M solution in hexanes). The mixture was stirred at -78°C for 40 min and a solution of 16.37 g (48.6 mmol) of ester **23** in 140 mL of tetrahydrofuran was added dropwise over a 25-min period. The resulting solution was stirred at -78°C for 3.5 h, poured into 1000 mL of saturated aqueous ammonium chloride and extracted with two 450-mL portions of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by column chromatography over 300 g of silica gel (eluted with 1600 mL of ethyl acetate-hexanes, 1:3) to afford 17.85 g (66%) of amine **24** as a pale yellow oil: IR (neat) 3341, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.63 (p, J = 6.6 Hz, 2H, CH_2), 2.48-2.83 (m, 8H, CHCO, CH_2N and NH), 3.56 (s, 4H, CH_2Ph), 3.65 (t, J = 6.3 Hz, 2H, CH_2O), 7.20-7.35 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ -5.3 (q), 18.3 (s), 26.0 (q), 28.1 (q), 33.2 (t), 45.4 (d), 46.7 (t), 50.4 (t), 54.3 (t), 58.5 (t), 61.5 (t), 80.3 (s), 126.9 (d), 128.1 (d), 129.0 (d), 139.1 (s), 173.8 (s); exact mass calcd. for $C_{31}H_{50}N_2O_3Si$ *m/e* 526.3593, found *m/e* 526.3546.

6-Benzyl 4-*tert*-butyl 2-benzyl-9-(*tert*-butyldimethylsiloxy)-2,6-diaza-1-phenyl-nonane-4,6-dicarboxylate (25). To a solution of 17.66 g (33.7 mmol) of amine **24** in 180 mL of tetrahydrofuran chilled in an ice bath was added 6.6 mL (47.2 mmol) of triethylamine and 6.0 mL (40.5 mmol) of benzyl chloroformate. The mixture was stirred at 0°C for 10 min, heated at reflux for 1.75 h, diluted with 500 mL of dichloromethane and washed with 500 mL of water. The aqueous wash was extracted with three 300-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by column chromatography over 300 g of silica gel (eluted with 800 mL of ethyl acetate-hexanes, 1:15 then with 910 mL of ethyl acetate-hexanes, 1:12 then with 770 mL of ethyl acetate-hexanes, 1:10) to afford 18.54 g (84%) of benzyl carbamate **25** as a pale yellow oil: IR (neat) 1726, 1704 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.68 (p, J = 6.4 Hz, 2H, CH_2), 2.43 (dd, J = 12.8, 5.5 Hz, 1H, CH_2N), 2.75 (dd, J = 12.8, 8.5 Hz, 1H, CH_2N), 2.92-3.43 (m, 1H, CHCO), 3.01-3.43 (m, 4H, CH_2NCO), 3.48-3.63 (m, 6H, NCH_2Ph and CH_2OSi), 5.05 (d, J = 12.7 Hz, 1H, OCH_2Ph), 5.12 (d, J = 12.7 Hz, 1H, OCH_2Ph), 7.21-7.39 (m, 15H, ArH); ^{13}C NMR (DMSO-d_6 at 373K) δ -6.1 (q), 17.2 (s), 25.1 (q), 27.1 (q), 30.5 (t), 44.0 (d), 44.4 (t), 47.5 (t), 53.5 (t), 57.4 (t), 59.8 (t), 65.7 (t), 79.4 (s), 126.2 (d), 126.8 (d), 127.0 (d), 127.4 (d), 127.6 (d), 128.1 (d), 136.4 (s), 138.3 (s), 154.7 (s), 171.8 (s); exact mass calcd. for $C_{39}H_{56}N_2O_5Si$ *m/e* 660.3961, found *m/e* 660.3960.

6-Benzyl 4-*tert*-butyl 2-benzyl-2,6-diaza-1-phenyl-9-nonanol-4,6-dicarboxylate (26). To a solution of 18.25 g (27.6 mmol) of silyl ether **25** in 100 mL of tetrahydrofuran chilled in an ice bath was added 41.5 mL (41.5 mmol) of a 1.0 M solution of *n*-tetrabutylammonium fluoride in tetrahydrofuran. The mixture was stirred at 0°C for 10 min, at room temperature for 2.25 h, diluted with 600 mL of dichloromethane and washed with 600 mL of water. The aqueous wash was extracted with three 200-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was purified by column chromatography over 150 g of silica gel (eluted with 1200 mL of ethyl acetate-hexanes, 1:2 then with 1000 mL of ethyl acetate-hexanes, 1:1) to afford 14.62 g (97%) of alcohol **26** as a colorless oil: IR (neat) 3464, 1724, 1702 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 1.41 (s, 9H, $C(CH_3)_3$), 1.65 (p, J = 7.0 Hz, 2H, CH_2), 2.43 (dd, J = 12.8, 5.5 Hz, 1H, CH_2N), 2.75 (dd, J = 12.8, 8.5 Hz, 1H, CH_2N), 2.91-3.02 (m, 1H, CHCO), 3.10-3.45 (m, 6H, CH_2NCO and CH_2O), 3.50 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.61 (d, J = 13.8 Hz, 2H,

NCH_2Ph), 4.03 (t, J = 5.0 Hz, 1H, OH), 5.05 (d, J = 12.7 Hz, 1H, OCH_2Ph), 5.12 (d, J = 12.7 Hz, 1H, OCH_2Ph), 7.20-7.36 (m, 15H, ArH); ^{13}C NMR (DMSO-d_6 at 373K) δ 27.2 (q), 30.6 (t), 44.1 (d), 44.5 (t), 47.4 (t), 53.5 (t), 57.4 (t), 58.0 (t), 65.7 (t), 79.4 (s), 126.2 (d), 126.8 (d), 127.0 (d), 127.4 (d), 127.6 (d), 128.1 (d), 136.5 (s), 138.3 (s), 154.8 (s), 171.9 (s); exact mass calcd. for $C_{26}H_{35}N_2O_5$ (M–C_7H_7) *m/e* 455.2548, found *m/e* 455.2542.

Benzyl [[2-(trimethylsilyl)ethyl]sulfonyl]carbamate (27). To a solution of 8.16 g (45.0 mmol) of 2-[(trimethylsilyl)ethyl]sulfonamide[24] in 61 mL of tetrahydrofuran stirred at -78°C was added 35 mL (45.0 mmol) of methyllithium (1.6 M solution in diethyl ether). The mixture was stirred at -78°C for 15 min, at 0°C for 25 min and 4.68 g (117 mmol) of 60% sodium hydride in mineral oil was added, followed by 6.7 mL (45.0 mmol) of *N,N,N,N*-tetramethylethylenediamine. The mixture was then recooled to -78°C and 9.2 mL (61.0 mmol) of benzyl chloroformate was added. The mixture was stirred at 0°C for 10 min, at room temperature for 21 h, cooled in an ice bath and quenched by slow addition of 25 mL of *tert*-butanol and enough water. The solution was acidified to pH 2 by addition of concentrated hydrochloric acid and extracted with four 100-mL portions of dichloromethane. The combined organic extracts were washed with 150 mL of brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (eluted with ethyl acetate-hexanes, 1:6 then 1:4) to afford 12.34 g (87%) of carbamate **27** as a pale yellow oil: IR (neat) 3237, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9H, $Si(CH_3)_3$), 0.98-1.04 (m, 2H, CH_2Si), 3.29-3.35 (m, 2H, CH_2SO_2), 5.20 (s, 2H, OCH_2), 7.36 (s, 5H, ArH); the NH proton was not observed; ^{13}C NMR ($CDCl_3$) δ -2.2 (q), 10.0 (t), 49.7 (t), 68.6 (t), 128.3 (d), 128.6 (d), 128.7 (d), 134.5 (s), 151.1 (s); exact mass calcd. for $C_{13}H_{21}NO_4SSi$ *m/e* 315.0961, found *m/e* 315.0962.

6,10-Dibenzyl 12-*tert*-butyl 14-benzyl-2,2-dimethyl-15-phenyl-5-thia-6,10,14-triaza-2-silapentadecane-6,10,12-tricarboxylate, 5,5-dioxide (28). To a solution of 6.01 g (11.0 mmol) of alcohol **26** and 5.17 g (16.4 mmol) of **27** in 270 mL of tetrahydrofuran chilled in an ice bath was added 6.50 g (24.7 mmol) of triphenylphosphine and, dropwise over a 5-min period, 3.2 mL (19.7 mmol) of diethyl azodicarboxylate. The orange solution was stirred at 0°C for 30 min, at room temperature for 3.5 h and concentrated in vacuo. The semi-solid residue was purified by column chromatography over 250 g of silica gel (eluted with 1350 mL of ethyl acetate-hexanes, 1:8 then with 1200 mL of ethyl acetate-hexanes, 1:7 then with 700 mL of ethyl acetate-hexanes, 1:6) to afford 8.69 g (94%) of sulfonamide **28** as a viscous pale yellow oil: IR (neat) 1731, 1714 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 0.02 (s, 9H, $Si(CH_3)_3$), 0.89-0.96 (m, 2H, CH_2Si), 1.40 (s, 9H, $C(CH_3)_3$), 1.86 (p, J = 7.3 Hz, 2H, CH_2), 2.43 (dd, J = 12.8, 5.6 Hz, 1H, CH_2N), 2.75 (dd, J = 12.8, 8.4 Hz, 1H, CH_2N), 3.06-3.40 (m, 5H, CHCO and CH_2N), 3.42-3.49 (m, 2H, CH_2SO_2), 3.51 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.61 (d, J = 13.8 Hz, 2H, NCH_2Ph), 3.62-3.68 (m, 2H, CH_2NSO_2), 5.03 (d, J = 12.6 Hz, 1H, OCH_2Ph), 5.12 (d, J = 12.6 Hz, 1H, OCH_2Ph), 5.26 (s, 2H, OCH_2Ph), 7.20-7.41 (m, 20H, ArH); ^{13}C NMR (DMSO-d_6 at 373K) δ -2.6 (q), 9.3 (t), 27.2 (q), 28.0 (t), 43.9 (d), 44.1 (t), 44.6 (t), 47.1 (t), 50.1 (t), 53.4 (t), 57.4 (t), 65.9 (t), 68.0 (t), 79.6 (s), 126.4 (d), 126.9 (d), 127.2 (d), 127.4 (d), 127.6 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.3 (d), 134.8 (s), 136.4 (s), 138.4 (s), 152.0 (s), 154.8 (s), 172.0 (s); exact mass calcd. for $C_{46}H_{61}N_3O_8SSi$ *m/e* 843.3951, found *m/e* 843.3978.

***tert*-Butyl hexahydro-2-thioxo-1-[3-[2-(trimethylsilyl)ethanesulfonamido]propyl]-5-pyrimidinecarboxylate (29).** A solution of 4.012 g (4.75 mmol) of **28** in 55 mL of anhydrous ethanol was degassed with argon for 15 min and 1.54 g of palladium hydroxide on carbon was added. The mixture was hydrogenated in a Parr hydrogenator under a 60 psi hydrogen pressure for 16 h, and filtered through a fritted glass. The catalyst was washed several times with ethanol and the filtrate was concentrated in vacuo. ^{1}H NMR analysis of the residue showed that cleavage of all four benzyl groups occured. To a solution of the residue in 40 mL of dichloromethane stirred at -78^{o}C was added dropwise over 1.5 h a solution of 1.415 g (7.13 mmol) of thiocarbonyldiimidazole in 35 mL of dichloromethane. The yellow solution was stirred at -78^{o}C for 30 min, allowed to warm up to room temperature over 1 h and heated at reflux for 17.5 h. The mixture was diluted with 250 mL of dichloromethane and washed with 100 mL of water. The aqueous wash was extracted with two 100-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The yellow semi-solid residue was purified by column chromatography over 35 g of silica gel (eluted with ethyl acetate-hexanes, 1:1) to afford 1.065 g (51%) of thiourea **29** as a white solid: mp 116-117^{o}C; IR (CH_2Cl_2) 1731, 1548 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 9H, $Si(CH_3)_3$), 1.02-1.08 (m, 2H, CH_2Si), 1.49 (s, 9H, $C(CH_3)_3$), 1.89 (p, J = 7.3 Hz, 2H, CH_2), 2.88-2.98 (m, 3H, CHCO and CH_2SO_2), 3.12-3.18 (m, 2H, CH_2NSO_2), 3.43-3.56 (m, 4H, CH_2N), 3.91-4.00 (m, 1H, CH_2N), 4.09-4.18 (m, 1H, CH_2N), 5.99 (br s, 1H, NH), 6.34 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.5 (t), 27.9 (q), 28.0 (t), 37.6 (d), 39.5 (t), 42.5 (t), 47.0 (t), 49.0 (t), 50.8 (t), 82.6 (s), 169.0 (s), 177.9 (s); exact mass calcd. for $C_{13}H_{26}N_3O_4S_2Si$ (M^+-C_4H_9) *m/e* 380.1136, found *m/e* 380.1114 and for $C_{13}H_{26}N_3O_3S_2Si$ (M^+-C_4H_9O) *m/e* 364.1187, found *m/e* 364.1167. Anal. calcd. for $C_{17}H_{35}N_3O_4S_2Si$: C, 46.65; H, 8.06. found C, 46.53; H, 8.11.

***tert*-Butyl 3,4,6,7,8,9-hexahydro-9-[[2-(trimethylsilyl)ethyl]sulfonyl]-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate (30).** To a solution of 1.053 g (2.41 mmol) of thiourea **29** in 15 mL of anhydrous methanol was added 185 mL (2.65 mmol) of iodomethane. The mixture was heated at 70^{o}C for 1 h and concentrated in vacuo. To a solution of the residual foam in 40 mL of dichloromethane was added 4.4 mL (3.27 g, 25 mmol) of *N,N*-diisopropylethyl amine. The mixture was heated at reflux for 20 h, diluted with 300 mL of cold diethyl ether and washed with 150 mL of cold 1M aqueous sodium hydroxide. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude oil was purified by column chromatography over 30 g of activity grade II basic alumina (eluted with dichloromethane-methanol, 200:1) to afford 0.790 g (81%) of guanidine **30** as a pale yellow oil: IR (neat) 1728, 1651, 1644, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9H, $Si(CH_3)_3$), 0.89-0.96 (m, 2H, CH_2Si), 1.42 (s, 9H, $C(CH_3)_3$), 1.94-2.04 (m, 2H, CH_2), 2.70-2.75 (m, 1H, CHCO), 3.11-3.25 (m, 3H, CH_2SO_2 and CH_2N), 3.33 (dd, J = 11.5, 8.7 Hz, 1H, CH_2N), 3.45 (dd, J = 14.7, 8.6 Hz, 1H, CH_2N), 3.53-3.68 (m, 4H, CH_2N), 3.72-3.77 (m, 1H, CH_2N); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.2 (t), 23.9 (t), 28.0 (q), 38.7 (d), 43.4 (t), 46.1 (t), 48.5 (t), 49.0 (t), 51.7 (t), 80.9 (s), 145.5 (s), 171.4 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_{17}H_{33}N_3O_4S_2Si$: 404.25 (M^++1, 100).

***tert*-Butyl octahydro-9-[[2-(trimethylsilyl)ethyl]sulfonyl]-9a*H*-pyrimido[1,2-*a*]-pyrimidin-3-carboxylate-9a-ylium chloride (31).** A stream of gaseous hydrochloric acid was passed through a solution of 1.057 g (2.62 mmol) of *tert*-butyl ester **30** in 46 mL of dichloromethane until saturation. The flask was then tightly closed and stored at 5°C for 24 h. The flask was opened and the mixture was allowed to warm up to room temperature over 1 h. At that point, a solid had precipitated and was collected on a Buchner funnel to afford 0.936 g (93%) of guanidine **31** as a white solid: mp; ^{1}H NMR (D_2O) δ 0.00 (s, 9H, $Si(CH_3)_3$), 0.92-0.98 (m, 2H, CH_2Si), 2.08 (m, 2H, CH_2), 3.20 (m, 1H, CHCO), 3.44-3.59 (m, 4H, CH_2N and CH_2SO_2), 3.62 (dd, *J* = 8.1, 5.1 Hz, 2H, CH_2N), 3.70 (d, *J* = 5.0 Hz), 2H, CH_2N); ^{13}C NMR (D_2O) δ -1.6 (q), 10.7 (t), 22.4 (t), 37.1 (d), 42.2 (t), 46.4 (t), 50.3 (t), 50.7 (t), 52.1 (t), 151.2 (s), 175.5 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_{13}H_{26}ClN_3O_4SSi$: 348.2 (M^+-HCl, 100). Anal. calcd for $C_{13}H_{26}ClN_3O_4SSi$: C, 40.66; H, 6.83. found C, 40.75; H, 6.78.

3,4,6,7,8,9-Hexahydro-9-[[2-(trimethylsilyl)ethyl]sulfonyl]-2*H*-pyrimi-do[1,2-*a*]pyrimidine-3-carboxylate, ester with [3-[*N*-[4-(carboxyamino)butyl]-16-hydroxy-hexadecanamido]propyl]carbamic acid, dibenzyl ester (32). To a solution of 182 mg (0.474 mmol) of guanidinium chloride **31** and 316 mg (0.474 mmol) of alcohol **9** in 6 mL of *N,N*-dimethylformamide was added 114 mg (0.520 mmol) of dicyclohexylcarbodiimide and 77 mg (0.620 mmol) of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 16 h, diluted with 150 mL of diethyl ether and washed with 50 mL of 1 M aqueous sodium hydroxide. The aqueous wash was extracted with two 80-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over 10 g of activity grade II basic alumina (eluted with dichloromethane-methanol, 300:1, then 250:1, then 200:1) to afford 305 mg (65%) of ester **32** as a pale yellow oil: IR (neat) 3343, 1725, 1633, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 9H, $Si(CH_3)_3$), 0.89-0.98 (m, 2H, CH_2Si), 1.17-1.35 (m, 18H, CH_2), 1.42-1.68 (m, 10H, CH_2), 1.70-1.82 (m, 2H, CH_2), 1.91-2.03 (m, 4H, CH_2), 2.22-2.26 (m, 2H, CH_2CO), 2.76-2.86 (m, 1H, CHCO), 3.06-3.28 (m, 8H, CH_2N and CH_2SO_2), 3.30-3.58 (m, 5H, CH_2N), 3.60-3.,75 (m, 5H, CH_2N), 4.08 (t, *J* = 7.0 Hz, 2H, CH_2OCO), 4.96 (br s, 1H, NH), 5.02-5.10 (m, 4H, $PhCH_2$), 5.78 (br s, 1H, NH), 7.27-7.37 (m, 10H, ArH); ^{13}C NMR (DMSO-d_6 at 373K) δ 1.2 (q), 19.8 (t), 23.9 (t), 24.57 (t), 24.62 (t), 24.8 (t), 25.0 (t), 27.6 (t), 28.1 (t), 28.3 (t), 28.4 (t), 28.5 (t), 31.8 (t), 32.9 (t), 35.8 (d), 37.3 (t), 46.2 (t), 47.0 (t), 64.5 (t), 64.77 (t), 64.83 (t), 127.0 (d), 127.1 (d), 127.8 (d), 136.9 (s), 150.4 (s), 155.6 (s), 169.6 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_{52}H_{84}N_6O_9SSi$: 997.7 (M^++1, 26.7), 554 (100).

3-Carboxyoctahydro-9a*H*-pyrimido[1,2-*a*]pyrimidin-9a-ylium chloride (19). To a suspension of 500 mg (1.31 mmol) of **31** in 10 mL of *N,N*-dimethylformamide was added 2.6 mL (2.6 mmol) of a 1 M solution of *n*-tetrabutylammonium fluoride in tetrahydrofuran. The resulting clear solution was heated at 80°C for 4 h. The precipitated solid was collected on a Buchner funnel, dissolved in 5 mL of 1 M aqueous hydrochloric acid and the resulting solution was concentrated in vacuo to afford, after drying, 285 mg (100%) of guanidinium chloride **19** as a white solid: mp 209-212.5°C; ^{1}H NMR (D_2O) δ 1.89 (p, *J* = 5.9 Hz, 2H, CH_2), 3.12 (p, *J* = 5.1 Hz, 1H, CHCO), 3.17 (dt, *J* = 5.8, 1.4 Hz, 2H, CH_2N), 3.24-2.32 (m, 2H, CH_2N), 3.43 (d, *J* = 4.0 Hz, 2H, CH_2N), 3.49 (m, 2H, CH_2N); ^{13}C NMR (D_2O) δ 20.2 (t), 36.4 (d), 38.0 (t), 39.4 (t), 46.9 (t), 47.4 (t), 150.8 (s), 174.6 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_8H_{14}ClN_3O_2$ 184 ((M^+-HCl)+1, 100).

3-Carboxyoctahydro-9a*H*-pyrimido[1,2-*a*]pyrimidin-9a-ylium chloride, ester with [3-[*N*-[4-(carboxyamino)butyl]-16-hydroxyhexadecanamido]propyl]carbamic acid, dibenzyl ester (33). To a solution of 125 mg (0.568 mmol) of guanidinium chloride **19** and 387 mg (0.568 mmol) of alcohol **9** in 3 mL of *N,N*-dimethylformamide was added 135 mg (0.682 mmol) of 3-[(dimethylamino)propyl]ethylcarbodiimide hydrochloride and 14 mg (0.114 mmol) of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 22 h and 193 mg (0.284 mmol) of alcohol **9** was added. After an additional 18 h of stirring, the mixture was diluted with 60 mL of dichloromethane and washed with 20 mL of 1M aqueous hydrochloric acid. The aqueous wash was extracted with 20 mL of dichloromethane. The combined organic extracts were washed with 40 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over 2 g of silica gel (eluted with dichloromethane-methanol, 20:1, then 5:1) to afford 315 mg of recovered starting alcohol **9**. Further elution afforded 254 mg (55%) of ester **33** as a colorless oil: IR (neat) 3296, 1729, 1714, 1651 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 1.25 (s, 22H, CH_2), 1.37-1.42 (m, 2H, CH_2), 1.49-1.55 (m, 4H, CH_2), 1.57-1.64 (m, 4H, CH_2), 1.84-1.96 (m, 2H, CH_2), 2.22 (t, J = 7.3 Hz, 2H, CH_2CO), 2.97-3.09 (m, 5H, CH_2N and CHCO), 3.14-3.57 (m, 12H, CH_2N), 4.10 (dt, J = 6.6, 4.1 Hz, 2H, CH_2OCO), 5.00 (d, J = 17.7 Hz, 2H, CH_2Ph), 5.04 (d, J = 17.7 Hz, 2H, CH_2Ph), 6.86 (br s, 2H, NH), 7.28-7.37 (m, 10H, ArH), 8.06 (br s, 1H, NH), 8.10 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6 at 373K) δ 19.8 (t), 24.5 (t), 24.8 (t), 26.4 (t), 27.6 (t), 28.0 (t), 28.26 (t), 28.31 (t), 28.36 (t), 28.42 (t), 31.8 (t), 35.8 (d), 37.1 (t), 37.9 (t), 38.66 (t), 38.73 (t), 39.8 (t), 46.1 (t), 46.8 (t), 46.9 (t), 64.4 (t), 64.7 (t), 64.8 (t), 127.0 (d), 127.1 (d), 127.7 (d), 136.89 (s), 136.94 (s), 150.6 (s), 155.6 (s), 169.5 (s), 171.3 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_{47}H_{73}N_6O_7Cl$: 834.8 ((M^+-HCl) +1, 100).

3-Carboxyoctahydro-9a*H*-pyrimido[1,2-*a*]pyrimidin-9a-ylium chloride, ester with [3-[*N*-(4-ammoniumbutyl)-16-hydroxyhexadecanamido]propyl]ammonium dichloride (2). To a solution of 68 mg (0.082 mmol) of **33** in 1.7 mL of ethanol was added 0.16 mL (1.63 mmol) of 1,4-cyclohexadiene and 68 mg of palladium on carbon. The mixture was heated at 60^oC for 3 h, filtered through a glass frit and 0.5 mL of a 0.8 M solution of hydrochloric acid in methanol was added. The solution was concentrated in vacuo to afford 37 mg (70%) of **2** as a pale yellow oil: IR (neat) 3288, 1732, 1648, 1644, 1633 cm^{-1}; ^1H NMR (DMSO-d_6 at 373K) δ 1.22-1.29 (m, 22H, CH_2), 1.50-1.60 (m, 8H, CH_2), 1.81-1.95 (m, 4H, CH_2), 2.28 (t, J = 7.2 Hz, 2H, CH_2CO), 2.80-2.90 (m, 5H, CH_2N and CHCO), 3.21-3.58 (m, 12H, CH_2N), 4.04-4.13 (m, 2H, CH_2OCO), 8.15-8.20 (m, 8H, NH); ^{13}C NMR (DMSO-d_6 at 373K) δ 19.8 (t), 23.9 (t), 24.5 (t), 24.8 (t), 27.6 (t), 28.1 (t), 28.3 (t), 28.4 (t), 28.5 (t), 31.8 (t), 35.8 (d), 37.1 (t), 38.1 (t), 38.7 (t), 46.1 (t), 46.9 (t), 64.4 (t), 150.6 (s), 169.6 (s); mass spectrum (FAB) *m/e* (relative intensity) molecular formula $C_{31}H_{63}N_6O_3Cl_3$: 565.6 ((M^+-3HCl) +1, 20), 149 (100).

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