Synthesis of Macrocyclic Insect-Derived Alkaloids

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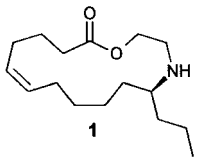
Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

Macrocyclic lactonic alkaloids found in the pupal secretions of two species of a coccinellid beetle (genus *Epilachna*) were prepared in enantiomerically pure form *via* an efficient synthetic route using enantiomerically pure α-amino acids as chiral-pool starting materials. Macrocycles with rings containing up to 98 atoms were synthesized in good yield using *Mukaiyama*'s macrolactonization conditions.

Introduction. – While 'natural-products' chemistry is, by most criteria, a mature field, the chemical ecological approach to natural-products chemistry continues to uncover structural novelty among the pheromones, allomones, and kairomones that govern a very wide range of biologically significant interactions in nature. The macrocyclic alkaloids, the synthesis of which is the subject of this communication, were, in fact, discovered as the result of a biorational investigation.

Since a pupating insect may be sessile for a period of up to a week or more, this stage in an insect's life cycle manifests a heightened risk of predation. It is not surprising, therefore, that the pupae of many beetle species possess protection in various forms, most commonly spines or concealing coloration [1], but in some cases chemical defenses as well. The pupae of several species of ladybird beetle (family Coccinellidae) are coated with glandular hairs, the tips of which secrete droplets of a clear liquid that repels predators. Analysis of the defensive secretion exuded by pupae of the Mexican bean beetle *Epilachna varivestis* revealed it to consist principally of the macrocyclic lactone epilachnene (=(5*Z*)-11-propyl-12-azatetradec-5-en-14-olide = (10*Z*)-5-propyl-1-oxa-4-azacyclopentadec-10-en-15-one; **1**) along with minor amounts of related compounds [2]. Encouraged by this interesting result, we undertook the analysis of the pupal defensive alkaloids of related coccinellids and found that the pupa of *Epilachna borealis* (the squash beetle) is protected by a much more complex exudate consisting of a combinatorial library of very-large-ring oligomeric alkaloids [3].



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These polyazamacrolides (PAMLs) are produced from an apparently random combination of the three homologous subunits (**2**, **3**, and **4**) which are present in a ratio of 90.5 : 8 : 1.5 (*Fig.*). The most abundant of these macrocyclic natural products consist of rings containing from three to seven of the subunits, with smaller amounts of cyclic dimers and higher oligomers containing up to fifteen subunits also present. The secretions from both *E. varivestis* and *E. borealis* have been shown to be repellent to foraging ants and spiders [2][3c,d].

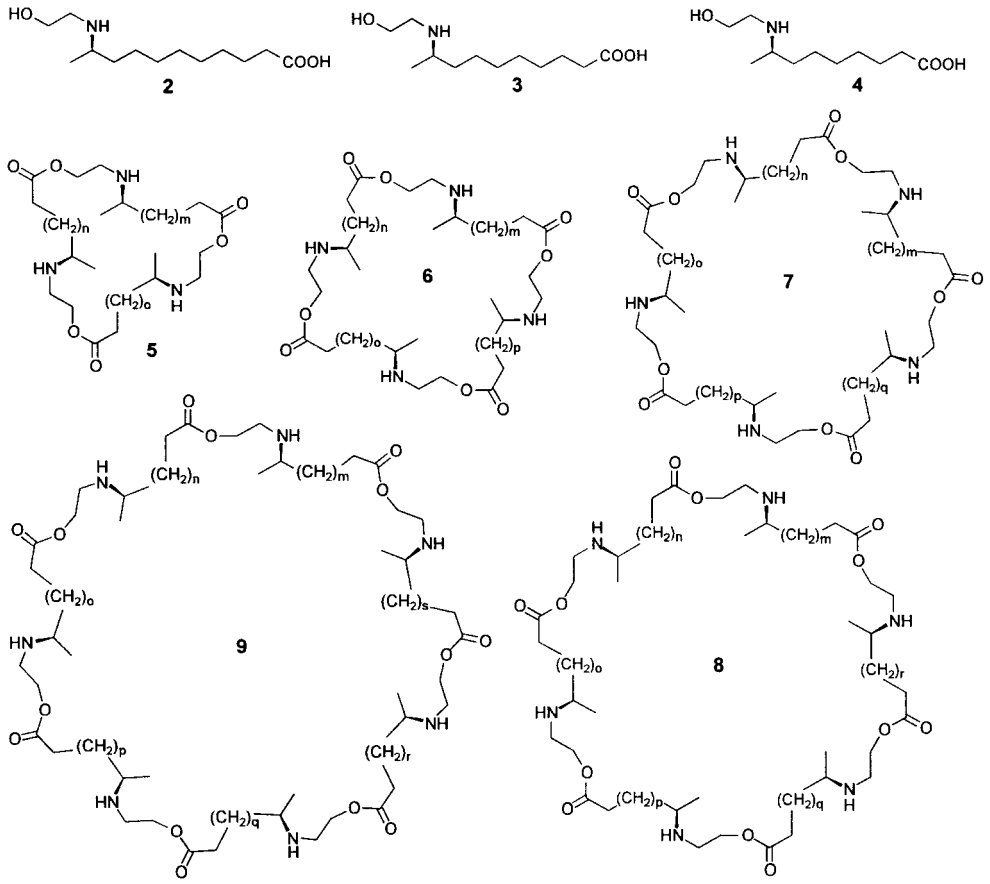


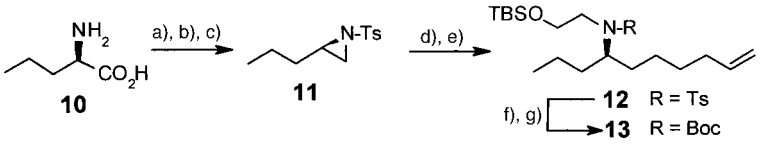
Figure. *(ω-1)-[(2-Hydroxyethyl)amino]alkanoic acids* **2**, **3**, *and* **4**, *the building blocks of the polyazamacrolides (PAMLs)* **5**–**9** *in* E. borealis. In these formulas, each of the variables *m* … *s* can have the values 5, 6, or 7.

Although insects are often sources of intriguing new structures, the quantities of any particular natural product available from an insect for chemical or biological studies is likely to be small. This is particularly true for components of complex mixtures; however, contemporary NMR and MS techniques are sufficiently powerful to lead to structural assignments on a micromolar scale, even without the necessity of prior separation and purification of each individual constituent (see, *e.g.*, [3b,e]). Consequently, synthesis becomes essential, not only to confirm spectroscopically deduced

molecular structure, but often to establish configuration, and to provide the only realistic source of new chemotypes for further study [4][5]. We here report the synthesis in enantiomerically pure form of epilachnene and of five representative PAMLs, with ring sizes ranging from 42 to 98 members, starting from readily available α-amino acids.

Results and Discussion. – *Synthesis of Epilachnene.* *N*-Tosylaziridine **11** was prepared in three steps from enantiomerically pure L-norvaline ((*S*)-2-aminopentanoic acid; **10**) by a procedure adapted from the literature [6]. Nucleophilic substitution at the less-substituted C-atom of the aziridine ring with the cuprate derived from di(pent-4-enyl)magnesium proceeded in good yield[2]). Deprotonation of the resulting sulfonamide was followed by alkylation with 1-bromo-2-[(*tert*-butyl)dimethylsilyloxy]-ethane to introduce the *N*-(2-hydroxyethyl) moiety in *O*-protected form. After reductive cleavage of the sulfonamide, the amine was protected as its (*tert*-butoxy)carbonyl (Boc) derivative **13** (*Scheme 1*)

Scheme 1



a) $LiBH_4$, Me_3SiCl, THF 0°. b) TsCl, pyridine, CH_2Cl_2, −20°, 40 h. c) K_2CO_3 acetone, r.t., 16 h. d) $(C_5H_9)_2Mg$, CuI, Et_2O. e) NaH, $TBSOCH_2Br$, DMF. f) Na, naphthalene, DME, −78 to −20°. g) Boc_2O, THF r.t., 4 h. TBS = (*t*-Bu)Me_2Si.

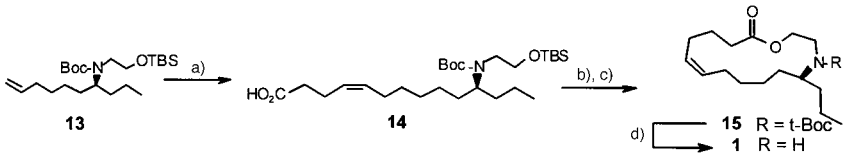
We originally envisioned ozonolysis of terminal alkene **13**, followed by reduction to provide the corresponding aldehyde, which could then be elaborated *via Wittig* olefination with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide to give alkenoic acid **14** (*Scheme 2*). This series of reactions proceeded as expected to give a moderate (*ca.* 60%) yield of **14**, with the disappointing overall yield due primarily to the surprising difficulty encountered in completely reducing the intermediate ozonide. Fortunately, a more efficient one-pot adaptation of this sequence could be developed in which the ozonide was treated directly with an excess of *Wittig* reagent. After ozonolysis of the alkene in cold (−78°) *tert*-butyl methyl ether, the resulting ozonide was simply titrated *in situ* with a THF solution of ylide until a persistent orange color was observed in the reaction mixture[3]). This one-pot procedure consistently provided the desired (*Z*)-alkene **14** in yields greater than 90%. Desilylation of **14** provided the ω-hydroxy acid needed for macrolactonization. The 15-membered ring of epilachnene (**1**) was formed in good yield (74%) using *Mukaiyama* reagent (2-chloro-1-methylpyridinium iodide) under high-dilution con-

[2]) Substitution with the cuprate derived from the *Grignard* reagent RMgX led to low yield due to competitive ring opening by X^-. Removal of the halide with 1,4-dioxane according to *Schlenk*'s procedure [7] ameliorated this difficulty.

[3]) It should be noted that this treatment of an ozonide with ylide does not require significantly more *Wittig* reagent than would generally be employed in the direct olefination of a carbonyl group, with 2.1 equiv. generally being sufficient to affect a complete transformation. For a discussion of a likely mechanism for this reaction, see [8].

ditions [9]. Gas-chromatographic analysis of the resulting macrocycle revealed the presence of 2–3% of the (5*E*)-diastereoisomer (a consequence of the formation of a small amount of (*E*)-product during the *Wittig* reaction). This impurity, which was found to have a slightly lower R_f than the desired (*Z*)-isomer, was readily removed by careful silica-gel chromatography. Acidic hydrolysis of the Boc protecting group in **15** then gave (–)-(*S*)-epilachnene quantitatively. The synthetic material was chromatographically and spectrometrically indistinguishable from an authentic insect-derived sample of the alkaloid.

Scheme 2



a) O_3, *t*-BuOMe, –78°, then $Ph_3P{=}CH(CH_2)_3CO_2K$ in THF. b) Bu_4NF, THF, r.t. c) 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN, reflux, 6 h, high dilution. d) CF_3CO_2H. TBS = (*t*-Bu)Me_2Si.

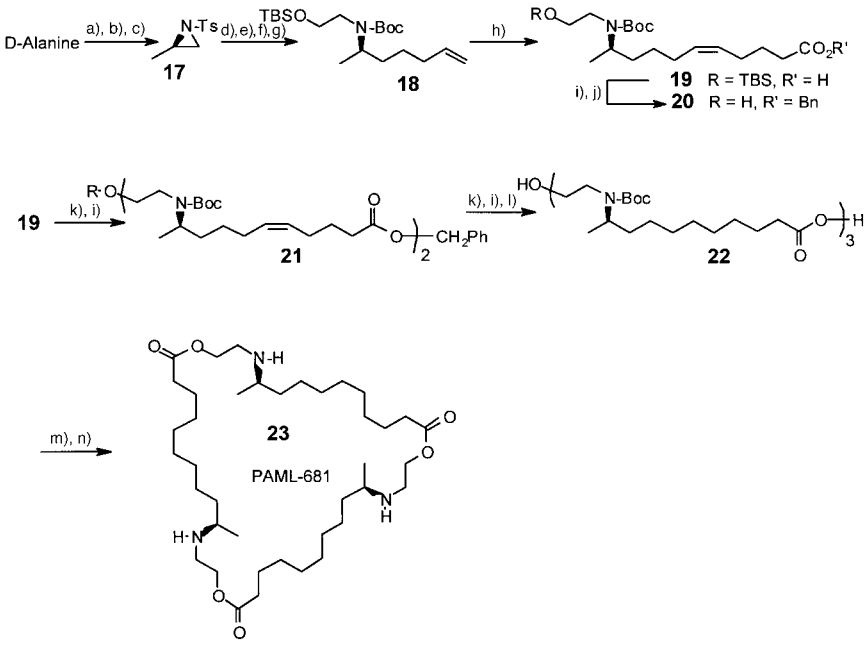
Synthesis of Polyazamacrolides. While the polyazamacrolides present in the exudate of *E. borealis* pupae comprise a complex mixture containing hundreds of related macrocyclic structures, we focused our synthetic efforts on producing the most abundant PAMLs present in the mixture: namely the macrocycles formed from three to seven units of the most abundant subunit **2**. These five compounds together comprise *ca*. 60% of the PAMLs present in the *E. borealis* pupal secretion.

Since these alkaloids are oligomers with ester bonds linking the subunits, a strategy predicated on a controlled iterative sequence of esterification and deprotection seems appropriate. The approach pursued is summarized in *Scheme 3*. We began by synthesizing the protected hydroxy acid **19** by a procedure analogous to that described above for the synthesis of the epilachnene precursor **14**. A portion of **19** was then elaborated to compound **20** bearing a free OH group and having the carboxy moiety protected as its benzyl ester. Compounds **19** and **20** thus have the complementary functionality required for an iterative esterification sequence. It should be noted that our choice of utilizing the same ozonolysis/*Wittig* olefination sequence we had employed in our synthesis of epilachnene to also produce the C_{11} chain of the PAML precursors, which may at first appear a rather inelegant solution owing to the introduction of a superfluous C=C bond, proves to be quite an efficient strategy, since the unnecessary C=C bonds are reduced concurrently with the hydrogenolysis of the benzyl ester later in the synthesis[4]).

Synthesis of the linear polymeric esters was a straightforward process. Polymers containing three to seven subunits were readily constructed *via* (DCC)-promoted esterification in the presence of 4-(dimethylamino)pyridine (DMAP). The sequence utilized for the synthesis of the trimeric compound PAML-681 (**23**) is presented in *Scheme 3*. Once the three subunits had been incorporated into the linear oligomer, this intermediate was desilylated and subjected to catalytic hydrogenation to afford the

[4]) In an earlier route (see [5]), we had explored opening the aziridine with a C_8 nucleophile, but the overall yield of such a sequence proved lower than that presented here.

Scheme 3



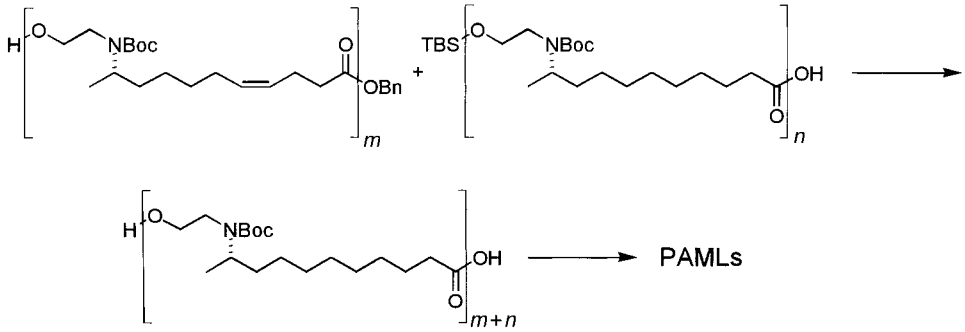
a) $LiBH_4$, Me_3SiCl, THF 0°. b) TsCl, pyridine, CH_2Cl_2, −20°, 40 h. c) K_2CO_3, acetone, r.t., 16 h. d) $(C_4H_7)_2Mg$, CuI, Et_2O. e) NaH, $TBSOCH_2CH_2Br$, DMF. f) Na^0, naphthalene, 1,2-dimethoxyethane (DME), −78 to −20°. g) Boc_2O, THF r.t., 4 h. h) O_3, *t*-BuOMe, −78°, then $Ph_3P{=}CH(CH_2)_3CO_2K$ in THF. i) BnOH, *N,N'*-dicyclohexylcarbodiimide (DCC), CH_2Cl_2. j) Bu_4NF, THF, r.t. k) **20**, DCC, DMAP, CH_2Cl_2. l) H_2, cat. 5% Pd/C, MeOH. m) 2-Chloro-1-methylpyridinium iodide, Et_3N, MeCN reflux, 6 h, high dilution. n) CF_3CO_2H. TBS = (*t*-Bu)Me_2Si.

saturated *ω*-hydroxy acid **22** needed for macrolactonization. To synthesize those PAMLs containing more than three monomeric units, we employed a convergent strategy wherein two complementary oligomeric intermediates were ligated to form the larger linear oligoester (*Scheme 4*).

We approached the cyclization step leading to the targeted very-large-ring lactones with some trepidation – while a number of efficient macrolactonization strategies are available, we are not aware of their having been applied to the formation of the unusually large rings (42 to 98 members) we desired. To our delight, the application of *Mukaiyama*'s reagent under highly dilute conditions proved quite successful, affording the 42-membered ring of PAML-681 in 72% yield. The yields were found to decrease modestly as the size of the ring being formed was increased. Nonetheless, even the cyclic heptamer containing a 98-membered ring was formed in a useful yield of 48% under these conditions.

Conclusion. – Efficient syntheses of epilachnene and five examples of the polyazamacrolides have thus been achieved; we have been able to produce sufficient quantities of these unique alkaloids to allow further study of their chemical and biological properties. It is our hope that the availability of synthetic samples of these

Scheme 4



PAML	*m*	*n*	Ring size	Lactonization yield
681	–	–	42	72%
908	2	2	56	65%
1135	2	3	70	63%
1362	3	3	84	56%
1589	3	4	96	48%

insect-derived alkaloids will also facilitate investigations into the ecology of *E. borealis*'s unusual combinatorial strategy of chemical defense.

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Experimental Part

General. Pyridine, Et_3N, and CH_2Cl_2 were distilled from CaH_2 and were re-distilled from 4-Å molecular sieves prior to use. 4-Bromobut-1-ene and 5-bromopent-1-ene were passed through a plug of freshly activated basic alumina prior to use. Et_2O, THF, *t*-BuOMe, 1,4-dioxane and 1,2-dimethoxyethane (DME) were distilled from potassium benzophenone ketyl prior to use. Other reagents were used as received from suppliers. Reactions were performed in dry glassware, which was evacuated and flushed with dry Ar prior to use, a slight positive pressure of Ar was maintained throughout the course of the reaction. Reactions run at low temp. were monitored internally and temp. reported are those measured in the reaction flask. Anal. TLC: on *Baker-flex* silica gel *IB2-F* precut plates visualized with UV light and/or one or more of the following stains: ninhydrin, anisaldehyde, ceric ammonium molybdenate, or basic potassium permanganate. Flash chromatography (FC): *EM Science* silica gel 60 (230–400 mesh ASTM) in *Ace Glassware* 150-mm long *Ace Thred*™ columns, with 15 psi dry He as a pressure source. Optical rotations: *Perkin Elmer 241* polarimeter, in a 10-mm × 100-mm sample cell; sample concentrations are expressed in g of sample per 100 ml of solvent. IR Spectra: *Hewlett-Packard HP 5965A* infrared detector (gas-phase spectra), or *Mattson Instruments Polaris* FT-infrared spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Varian XL-500* and *XL-400* spectrometers; chemical shifts δ in ppm downfield of 0 ppm as established by the ^{1}H or ^{13}C shift of the solvent used, relative to TMS (C_6D_6, 7.16/128.39 ppm; $CDCl_3$; 7.26/77.23 ppm; CD_3OD, 5.39/49.15 ppm; $(CD_3)_2CO$ 2.05/29.92 ppm). Low-resolution MS: *HP 5890 II* gas chromatograph linked to an *HP 5970* mass-selective detector, or with a *Micromass Quattro I* mass spectrometer operated in positive-ion electrospray mode; high-resolution (HR) and low-resolution CI-MS were obtained at the Illinois Mass Spectrometry Laboratory with a *VG ZAB-SE* or *VG 70-VSE* instrument.

(−)-(2S)-2-Aminopentan-1-ol. Me_3SiCl (22 ml, 0.172 mol) was added slowly to a stirred THF (40 ml) soln. of $LiBH_4$ (1.86 g, 86 mmol) at 0°. After stirring for 30 min, D-norvaline (5.0 g, 43 mmol) was added portionwise over 10 min. The mixture was allowed to warm to r.t. and stirred for 16 h, then it was cooled to 0° and quenched by the cautious addition of MeOH (20 ml). After 30 min of stirring, the volatiles were removed by short-path

distillation. The remaining solid white residue was taken up in 30 ml of 20% aq. KOH soln. and extracted with CH_2Cl_2 (5×25 ml). The org. extracts were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a white solid (3.88 g), which was purified by distillation at reduced pressure (110°/2 mm Hg) to give 3.38 g (32.8 mmol, 76%) of a crystalline white solid. M.p. 41–43°. $[\alpha]_D^{25} = -6.0$ ($c = 1.0$, MeOH); IR (gas phase): 3672, 3565, 2936, 2884, 1620.5, 1270, 1047, 790. ^{1}H-NMR (500 MHz, C_6D_6): 3.45 (*dd*, $J = 10.1$, 3.5, 1 H); 3.15 (*dd*, $J =$ 10.1, 7.8, 1 H); 2.52 (*m*, 1 H); 1.80 (br. *s*, 3 H); 1.25–1.05 (*m*, 3 H); 0.99–0.91 (*m*, 1 H); 0.79 (*t*, $J = 7.1$, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): 67.17; 53.22; 37.29; 19.85; 14.7.

*(+)-(2S)-2-[(*p*-Tolylsulfonyl)amino]-1-[(*p*-tolylsulfonyl)oxy]pentane*. To a stirred CH_2Cl_2 soln. of (−)-(2*S*)-2-aminopentan-1-ol (2.80 g, 27 mmol in 100 ml) at −20° was added 7 ml (80 mmol) of dry pyridine, followed by 11.4 g (60 mmol) of TsCl. The soln. was allowed to warm to r.t. and stirred for 30 h. The mixture was then poured into 200 ml of 1N HCl and extracted with CH_2Cl_2 (3×100 ml). Each org. layer was subsequently washed with 100 ml of sat. aq. $NaHCO_3$ soln. The org. fractions were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 12.3 g of a viscous yellow oil. Purification by FC (50 mm × 12″ column, eluted with 10% (*v*/*v*) hexane/CH_2Cl_2) gave 9.9 g (24 mmol, 89%) of a white solid. M.p. 65–67°. $[\alpha]_D^{25} = -48.7$ ($c = 1.0$, MeOH). IR (gas phase): 3415, 3024, 2976, 2938, 1601, 1409, 1357, 1168, 1095, 813. ^{1}H-NMR (500 MHz, C_6D_6): 7.76–7.72 (*m*, 4 H); 6.80–6.77 (*m*, 2 H); 6.76–6.63 (*m*, 2 H); 4.50 (*d*, $J = 3.5$, 1 H); 3.83 (*dd*, $J = 10.2$, 3.3, 1 H); 3.77 (*dd*, $J = 10.1$, 4.5); 3.3–3.23 (*m*, 1 H); 1.88 (*s*, 3 H); 1.84 (*s*, 3 H); 1.17–1.09 (*m*, 1 H); 1.03–0.95 (*m*, 1 H); 0.94–0.84 (*m*, 1 H); 0.80–0.69 (*m*, 1 H); 0.51 (*t*, $J = 7.0$). ^{13}C-NMR (101 MHz, C_6D_6): 144.95; 143.37; 139.25; 133.95; 130.34; 130.04; 128.27; 127.76; 72.00; 52.84; 34.08; 21.54; 21.48; 19.06; 13.85.

*(−)-(2S)-2-Propyl-1-(*p*-tolylsulfonyl)aziridine* (**11**). To a stirred slury of anh. K_2CO_3 (4.56 g, 33 mmol) in acetone (50 ml) was added 6.70 g (16.3 mmol) of (−)-(2*S*)-2-[(*p*-tolylsulfonyl)amino]-1-[(*p*-tolylsulfonyl)-oxy]pentane. This mixture was stirred at r.t. for 15 h, then filtered and concentrated *in vacuo* to afford 4.3 g of a colorless oil, which was purified by FC (50 mm × 6″ column, eluted with 12% (*v*/*v*) hexane/CH_2Cl_2) to give 3.68 g (15.4 mmol, 94%) of **11**. Colorless oil. $[\alpha]_D^{25} = +13.8$ ($c = 4.7$, MeOH). IR (gas phase): 3072, 2928, 2885, 1351, 1170, 1094, 948. ^{1}H-NMR (500 MHz, C_6D_6): 7.91–7.88 (*m*, 2 H); 6.76–6.73 (*m*, 2 H); 2.65 (*m*, 1 H); 2.19 (*d*, $J = 7.0$, 1 H); 1.84 (*s*, 3 H); 1.50 (*d*, $J = 4.5$, 1 H); 1.15–1.03 (*m*, 3 H); 1.03–0.95 (*m*, 1 H); 0.66 (*t*, $J = 7$, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): 144.19; 13.99; 137.23; 129.95; 128.68; 40.19; 33.88; 33.85; 21.49; 20.63.

*(+)-(7S)-7-[(*p*-Tolylsulfonyl)amino]dec-1-ene. Formation of Dialkyl Magnesium Reagent*. Mg Powder (1.52 g, 60 mmol) and 20 ml of dry Et_2O were placed in a 3-neck flask, fitted with a N_2 inlet, septum, and attached *via* a 25–50 μm glass frit to a second two-neck flask. To this vigorously stirred suspension, was added 5-bromopent-1-ene (6.0 ml, 50 mmol) over a period of 1 h *via* mechanical syringe pump. After the addition was complete, the mixture was stirred for an additional 40 min before 4.5 ml of dry 1,4-dioxane (50 mmol) was added slowly over 15 min, resulting in the formation of a thick white precipitate. The dialkylmagnesium soln. was filtered from this solid by forcing the reaction mixture through the glass frit under N_2 pressure into the second flask, giving a clear, light yellow soln. The original reaction flask and the precipitate were rinsed wtih dry Et_2O (2×10 ml), which was also forced through the frit into the collection flask.

b) *Alkylation of Aziridine* **11**. A slurry of CuI (1.42 g, 7.5 mmol) in Et_2O (10 ml) was cooled to −70°. All of the above alkylmagnesium soln. was then added slowly *via* cannula. The cold bath was removed, and the mixture was allowed to warm to −26°, whence a pronounced color change from light tan to a dark maroon occurred. The cold bath was replaced, and the mixture was again cooled to −70°. Aziridine **11** (3.0 g, 12.5 mmol) was then added in one portion. The mixture was allowed to warm slowly to r.t. and then stirred for 9 h. The mixture was quenched by the careful addition of 20 ml of sat. aq. NH_4Cl soln. The contents of the reaction flask were then poured into a separatory funnel containing 125 ml of a 1:1 mixture of sat. aq. NH_4Cl and sat. aq. NH_4OH solns. The aq. layer was separated and extracted with ether (3×200 ml), the org. extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil (4.3 g), which was purified by flash chromatography (50 mm × 6″ column, eluted with 15% (*v*/*v*) hexane/CH_2Cl_2) to give 3.63 g (11.7 mmol, 94%) of a clear, colorless oil. $[\alpha]_D^{25} = +0.18$ ($c = 0.9$, MeOH). IR (vapor phase): 3407, 3084, 2938, 2877, 1641, 1600, 1495, 1414, 1359, 1167, 1094, 1016, 917, 813. ^{1}H-NMR (500 MHz, C_6D_6): 7.89–7.87 (*m*, 2 H); 6.83–6.80 (*m*, 2 H); 5.62 (*ddt*, $J = 16.8$, 10.1, 6.7, 1 H); 5.01–4.95 (*m*, 2 H); 4.66 (*d*, $J = 8.5$, 1 H); 3.24 (*m*, 1 H); 1.91 (*s*, 3 H); 1.86–1.81 (*m*, 2 H); 1.23–0.95 (*m*, 10 H); 0.73 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): 142.89; 140.39; 139.31; 129.90; 127.82; 114.92; 54.24; 37.93; 35.53; 34.30; 29.37; 25.41; 21.45; 19.21; 14.39.

*(+)-(7S)-7-({2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}(*p*-tolylsulfonyl)amino)dec-1-ene* (**12**). (+)-(6*S*)-6-[(*p*-Tolylsulfonyl)amino]dec-1-ene (2.95 g, 9.5 mmol) was added to a stirred slurry of NaH (342 mg, 14.3 mmol) in 20 ml of dry DMF at 0° by syringe pump over a period of 1 h. The mixture was stirred for an additional 30 min after addition was complete, then 3.4 g (14.2 mmol) of 1-bromo-2-[(*tert*-butyl)dimethylsiloxy]ethane was added dropwise. The mixture was allowed to warm to r.t. and stirred for 72 h. After addition of 30 ml of H_2O, the

mixture was extracted with hexane/Et_2O 9:1 (*v*/*v*, 3 × 30 ml). The combined org. extracts were washed with brine (1 × 30 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 3.1 g of a yellow oil, which was purified by FC (50 mm × 6″ column eluted with 6% (*v*/*v*) AcOEt/hexane) to give 4.25 g (9.1 mmol, 95%) of **12**. Clear, colorless oil. $[\alpha]_D^{25} = -1.4$ (*c* = 4.4, MeOH). IR (gas phase): 3085, 2961, 2939, 2871, 1471, 1357, 1262, 1164, 1098, 914, 839. ^{1}H-NMR (500 MHz, C_6D_6): 7.78–7.74 (*m*, 2 H); 6.79–6.73 (*m*, 2 H); 5.73 (*ddt*, *J* = 16.9, 10.3, 6.7, 1 H); 5.04–4.97 (*m*, 2 H); 4.09–4.00 (*m*, 2 H); 3.75 (*quint.*, *J* = 7.0, 1 H); 3.31–3.19 (*m*, 2 H); 1.90–1.84 (*m*, 2 H); 1.89 (*s*, 3 H); 1.32–1.06 (*m*, 10 H); 1.10–1.02 (*m*, 1 H); 0.99 (*s*, 9 H); 0.79 (*t*, *J* = 7.2, 3 H); 0.145 (*s*, 3 H); 0.143 (*s*, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): −4.77; 14.47; 18.87; 20.66; 21.41; 26.52; 29.49; 33.95; 34.28; 36.45; 45.92; 59.01; 64.23; 115.00; 127.99; 129.87; 139.26; 139.55; 142.91. EI-MS: 384 (5), 272 (100), 256 (8), 184 (42), 155 (50), 91 (61), 73 (54). HR-MS: 384.20303 ($C_{25}H_{45}NO_3SSi^+$; calc. 384.20309).

*(+)-(7S)-7-({[2-(*tert*-Butyl)dimethylsilyloxy]ethyl}amino)dec-1-ene.* a) *Formation of Sodium Naphthalide Soln.* To a stirred soln. of naphthalene (190 mg, 1.5 mmol) in 10 ml of dry DME was added Na metal (125 mg, 5.5 mmol). This mixture was stirred vigorously for 2 h at r.t. prior to use.

b) *Deprotection of* p-*Toluenesulfonate*. A soln. of **12** in 5 ml of dry 1,2-dimethoxyethane (DME) was cooled to −50°, and the above naphthalide soln. was added dropwise with vigorous stirring. Addition (*ca*. 5 ml) was continued until a persistent green color was achieved. The mixture was allowed to warm to 0° and then quenched by addition of 1 ml of EtOH. The mixture was concentrated at reduced pressure to give a solid white residue, which was purified by FC (15 mm × 6″ column, eluted with 5% (*v*/*v*) AcOEt/hexane, followed by 20% AcOEt/hexane containing 1% Et_3N) to afford 60 mg (0.19 mmol, 94%) of a slightly yellow oil. $[\alpha]_D^{25} = +2.0$ (*c* = 2.4, MeOH). IR (gas phase): 3740, 3084, 2364, 2329, 1652, 1267, 888. ^{1}H-NMR (500 MHz, C_6D_6): 5.78 (*ddt*, *J* = 17.0, 10.1, 6.7, 1 H); 5.04 (*dq*, *J* = 17.1, 1.7, 1 H); 5.01 (*ddt*, *J* = 10.1, 2.3, 1.2, 1 H); 3.70 (*t*, *J* = 5.37, 2 H); 2.71 (*t*, *J* = 5.3, 2 H); 2.58–2.52 (*m*, 1 H); 2.06–2.05 (*m*, 2 H); 1.45–1.34 (*m*, 10 H); 0.97 (*s*, 9 H); 0.94 (*t*, *J* = 7.2, 3 H); 0.08 (*s*, 6 H). ^{13}C-NMR (101 MHz, $CDCl_3$): 139.16; 114.51; 62.39; 57.39; 49.09; 36.38; 33.97; 33.92; 29.42; 26.08; 25.41; 19.13; 18.42; 14.53; −5.14.

*(7S)-(+)-7-([(*tert*-Butoxy)carbonyl]{[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)dec-1-ene* (**13**). To a stirred soln. of (+)-(7*S*)-7-({2-[(*tert*-butyl)dimethylsiloxy]ethyl}amino)dec-1-ene (127 mg, 0.41 mmol) in THF (4 ml) was added di(*tert*-butyl) dicarbonate (97 mg, 0.44 mmol). The soln. was allowed to stir at r.t. for 10 h, then quenched with sat. aq. NH_4OH soln. (1 ml) and allowed to stir for an additional 30 min. After addition of 50 ml of H_2O, the mixture was extracted with Et_2O (3 × 40 ml). The combined org. extracts were rinsed with brine (30 ml), dried (K_2CO_3), filtered, and concentrated to give 194 mg of a colorless oil, which was purified by FC (15 mm × 6″ column eluted with 10% (*v*/*v*) AcOEt/hexane) to afford 162 mg (0.39 mmol, 97%) of **13**. Colorless oil. $[\alpha]_D^{25} = +2.3$ (*c* = 4.4, MeOH). IR (gas phase): 3084, 2964, 2938, 2870, 2364, 2329, 1707, 1464, 1396, 1279, 1175, 1105, 916, 838. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 5.86–5.76 (*m*, 1 H); 5.08–4.97 (*m*, 2 H); 4.28 (br. *s*, 0.5 H); 3.98 (*t*, *J* = 7.3, 1 H); 3.86 (*t*, *J* = 7.3, 1 H); 3.32 (*td*, *J* = 6.9, 1.5, 1 H); 3.23 (*td*, *J* = 7.3, 2.0, 1 H); 1.97 (*quint.*, *J* = 6.4, 2 H); 1.48 (*s*, 4.5 H); 1.46 (*s*, 4.5 H); 1.43–1.10 (*m*, 10 H); 0.99 (*s*, 9 H); 0.89 (*t*, *J* = 6.9, 1.5 H); 0.88 (*t*, *J* = 6.9, 1.5 H); 0.139 (*s*, 3 H); 0.125 (*s*, 3 H). EI-MS: 340 (4), 300 (100), 270 (21), 168 (24), 162 (24), 144 (15), 100 (18), 57 (100). HR-MS: 413.33219 ($C_{23}H_{47}NO_3Si^+$; calc. 413.33252).

*(+)-(5Z,11S)-11-{[(*tert*-Butoxy)carbonyl]([2-[(*tert*-butyl)dimethylsilyloxy]ethyl)amino}tetradec-5-enoic Acid* (**14**). a) *Formation of Ylide*. To a stirred slurry of (4-carboxybutyl)triphenylphosphonium bromide (887 mg, 2.0 mmol) in 6 ml of dry THF was added 4.0 ml of a 1.0M soln. of potassium salt of hexamethyldisilazane (KHMDS) in THF. The mixture was stirred vigorously for 1 h at r.t. After centrifugation, the clear, deep orange ylide soln. was separated from the solids by syringe.

b) *Ozonolysis*/Wittig *Reaction*. A soln. of **13** (162 mg, 0.39 mmol) in 6 ml of *t*-BuOMe was cooled to −76°. While stirring vigorously, a stream of O_3 in O_2 was bubbled through the soln. until a faint blue color was detected. The mixture was swept with Ar for 10 min to remove excess O_3 and O_2. The above ylide soln. was then added dropwise to the stirred soln. until a persistent orange color was achieved. Subsequently, the cooling bath was removed. After warming to r.t., the mixture was stirred for an additional 2 h, before being quenched by the addition of 1 ml of AcOH. The mixture was poured into 20 ml of 1N HCl and extracted with Et_2O (5 × 20 ml). The combined org. layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 250 mg of a yellow oil, which was purified by FC (15 mm × 6″ column, eluted with 15% (*v*/*v*) AcOEt/hexane containing 1% of AcOH) to afford 176 mg (0.36 mmol, 92%) of **14**. Viscous, colorless oil. $[\alpha]_D^{25} = +2.9$ (*c* = 2.0, MeOH). ^{1}H-NMR (500 MHz, CD_3OD; mixture of conformers): 5.45–5.34 (*m*, 2 H); 4.04 (br. *s*, 0.5 H); 3.88 (br. *s*, 0.5 H); 3.73 (*t*, *J* = 7.1, 1 H); 3.69 (*t*, *J* = 7.0, 1 H); 3.15 (*t*, *J* = 7.1, 1 H); 3.10 (*t*, *J* = 7.1, 1 H); 2.28 (*t*, *J* = 7.4, 2 H); 2.14–2.00 (*m*, 4 H); 1.65 (*quint.*, *J* = 7.4, 2 H); 1.61–1.50 (*m*, 1 H); 1.49–1.40 (*m*, 1 H); 1.47 (br. *s*, 4.5 H); 1.45 (br. *s*, 4.5 H); 1.46–1.22 (*m*, 9 H); 0.95–0.91 (*m*, 3 H); 0.92 (*s*, 4.5 H); 0.91 (*s*, 4.5 H); 0.088 (*s*, 3 H); 0.083 (*s*, 3 H). ^{13}C-NMR (101 MHz, CD_3OD; mixture of conformers): 179.5; 142.9 (0.5 C); 137.8 (0.5 C); 130.7 (0.5 C); 129.4;

128.4; 127.1; 63.1; 58.5; 44.9; 35.6; 33.3; 33.2; 29.4; 26.9; 26.36; 26.34; 25.9; 24.5; 21.4; 19.9; 18.3; 13.8; −5.3. CI-MS (CH_4): 500 (5, $[M+H]^+$), 445 (2), 428 (23), 400 (100), 398 (12), 386 (20), 368 (12), 342 (11), 254 (9), 230 (9), 57 (20). HR-MS (CI): 500.37577 ($C_{27}H_{51}NO_5Si^+$; calc. 500.37571).

*(+)-(5Z,11S)-11-{[(*tert*-Butoxy)carbonyl](2-hydroxyethyl)amino}tetradec-5-enoic Acid*. To a stirred soln. of **14** (174 mg, 0.35 mmol) in THF (1 ml) was added 0.38 ml of a 1M THF soln. of Bu_4NF. The mixture was stirred at r.t. for 4 h, then concentrated, and purified by FC (15 mm × 6″ column, eluted with 40% (*v*/*v*) AcOEt/hexane containing 0.5% AcOH) to give 124 mg (0.32 mmol, 92%) of a colorless oil. $[\alpha]_D^{25} = +1.97$ ($c = 4.6$, MeOH). ^{1}H-NMR (500 MHz, CD_3OD; mixture of conformers): 5.44–5.32 (*m*, 2 H); 4.0 (br. *s*, 0.5 H); 3.8 (br. *s*, 0.5 H); 3.63–3.58 (*m*, 2 H); 3.16 (*t*, $J = 6.7$, 1 H); 3.12–3.08 (*m*, 1 H); 2.28 (*t*, $J = 7.4$, 2 H); 2.12–2.02 (*m*, 4 H); 1.64 (*quint.*, $J = 7.0$, 2 H); 1.52 (br. *s*, 1 H); 1.47 (*s*, 4.5 H); 1.46 (*s*, 4.5 H); 1.46–1.22 (*m*, 9 H); 0.96 (*t*, $J = 7.3$, 1.5 H); 0.93 (*t*, $J = 7.4$, 1.5 H). ^{13}C-NMR (101 MHz, C_6D_6; mixture of conformers): 178.2; 173.3; 123.4; 131.8; 130.4; 129.7; 79.29; 65.07; 64.65; 36.17; 34.0; 32.15; 30.13; 28.94; 28.87; 27.67; 26.36; 24.05; 20.57; 14.7. CI-MS (CH_4): 386 (3, $[M+H]^+$), 342 (3), 314 (16), 294 (32), 287 (19), 286 (100), 284 (11), 268 (16), 254 (8), 242 (16), 116 (18), 57 (25). HR-MS (CI): 386.29049 ($C_{21}H_{39}NO_5^+$; calc. 386.29065).

*(−)-(5S,10Z)-4-[(*tert*-Butoxy)carbonyl]-5-propyl-1-oxa-4-azacyclopent-10-en-15-one* (**15**). Over a period of 1 h, a mixture of (+)-(5*Z*,11*S*)-11-{[(*tert*-butoxy)carbonyl](2-hydroxyethyl)amino}pentadec-5-enoic acid (111 mg, 0.29 mmol) and Et_3N (0.32 ml, 2.3 mmol) in 10 ml MeCN was added *via* mechanical syringe pump to a refluxing MeCN soln. of 2-chloro-1-methylpyridinium iodide (295 mg, 1.15 mmol in 100 ml). Reflux was continued for 30 min after addition was complete. The mixture was then concentrated *in vacuo*, taken up in 10 ml of H_2O, and extracted with Et_2O (3 × 10 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 120 mg of a yellow residue, which was purified by FC (11 mm × 6″ column, eluted with 10% (*v*/*v*) AcOEt/hexane) to give 77 mg (21 mmol, 72% yield) of **15**. Colorless oil. $[\alpha]_D^{25} = -6.0$ ($c = 2.05$, MeOH). ^{1}H-NMR ($CDCl_3$, mixture of conformers): 5.44–5.16 (*m*, 2 H); 4.31–4.06 (*m*, 3 H); 3.45 (br. *s*, 1 H); 3.2 (br. *s*, 1 H); 2.34 (*t*, $J = 7.2$, 2 H); 2.20–1.90 (*m*, 4 H); 1.88–1.64 (*m*, 3 H); 1.44 (br. *s*, 9 H); 1.42–1.08 (*m*, 7 H); 0.88 (*t*, $J = 7.2$, 3 H). EI-MS: 367 (2), 324 (10), 294 (12), 267 (32), 252 (14), 225 (92), 224 (100), 208 (10), 170 (33), 157 (15), 142 (15), 140 (18), 97 (50), 84 (24), 57 (100). HR-MS (CI): 367.27241 ($C_{21}H_{37}NO_4^+$; calc. 367.27225).

(+)-(5S,10Z)-5-Propyl-1-oxa-4-azacyclopentadec-10-en-15-one ((*S*)-Epilachnene; **1**). A sample of **15** (5.0 mg, 13.6 μmol) was taken up in 50 μl of CF_3COOH and allowed to sit for 15 min. The excess acid was removed at reduced pressure, and the residue was taken up in 20% aq. K_2CO_3 (0.5 ml) and extracted with Et_2O (3 × 0.5 ml). The combined org. fractions were passed through a plug of anh. K_2CO_3 and concentrated *in vacuo* to afford 3.6 mg (13.4 μmol, 99%) of pure **1**. $[\alpha]_D^{25} = +50.8$ ($c = 1.36$, MeOH). IR (gas phase): 3008.6, 2967.8, 2937.7, 2363.7, 2328.9, 1752.4, 1709.6, 1457.8, 1370.3, 1236.5, 1153.8, 1051.3. ^{1}H-NMR (500 MHz, C_6D_6): 5.39 (*dtt*, $J = 10.9$, 7.9, 1.8, 1 H); 5.21 (*dddt*, $J = 11.0$, 7.6, 6.1, 1.3, 1 H); 4.17 (*ddd*, $J = 11.2$, 7.4, 2.3, 1 H); 3.85 (*dd*, $J = 11.2$, 6.6, 2.4, 1 H); 2.68 (*ddd*, $J = 13.9$, 7.4, 2.4, 1 H); 2.49 (*ddd*, $J = 13.9$, 6.6, 2.3, 1 H); 2.31 (*m*, 1 H); 2.26–2.18 (*m*, 1 H); 2.20 (*ddd*, $J = 16.5$, 9.0, 3.4, 1 H); 2.15 (*ddd*, $J = 16.5$, 7.8, 3.5, 1 H); 2.16–2.08 (*m*, 1 H); 2.02–1.96 (*m*, 2 H); 1.67 (*ddddd*, $J = 13.9$, 9.2, 6.6, 5.9, 3.5, 1 H); 1.54 (*ddddd*, $J = 13.9$, 8.2, 7.9, 5.9, 3.4, 1 H); 1.41–1.05 (*m*, 10 H); 0.94–0.89 (*t*-like *m*, 3 H). ^{13}C-NMR (C_6D_6, 100 MHz): 172.9; 131.5; 129.8; 63.7; 56.4; 45.8; 35.5; 34.6; 31.9; 29.2; 27.8; 27.7; 25.9; 24.2; 19.2; 14.6. EI-MS (rel. int.): 267 (20), 252 (11), 224 (100), 170 (15), 157 (5), 140 (6), 116 (5), 97 (14). HR-MS: 267.219856 ($C_{16}H_{29}NO_2^+$; calc. 267.219829).

*(+)-(2S)-2-Methyl-1-(*p-*tolylsulfonyl)aziridine* (**17**). A 50-ml pear-shaped flask was charged with a mixture of TsCl (4.19 g, 22 mmol), pyridine (3.5 ml), and CH_2Cl_2 (6.5 ml). The mixture was cooled to 0°, and (−)-(2*S*)-2-aminopropan-1-ol (0.751 g, 10.0 mmol) was added dropwise. The mixture was allowed to warm to r.t. and stirred for 16 h. The mixture was then poured into a separatory funnel containing 50 ml of cold 1N HCl and 25 ml of CH_2Cl_2. After extraction, the org. layer was separated and washed with sat. $CuSO_4$ soln. (1 × 25 ml) and brine (1 × 25 ml); each aq. layer was back-extracted with CH_2Cl_2 (2 × 25 ml). The org. fractions were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give 3.9 g of a greenish oil, which was taken up in dry acetone (50 ml) and stirred over 5.0 g of K_2CO_3 for 14 h. This mixture was filtered through a plug of *Celite* and concentrated *in vacuo* to give 3.4 g of a yellow oil, which was purified by FC (50 mm × 6″ column, eluted with 18% (*v*/*v*) AcOEt/hexane) to give 1.99 g of a white solid, which was recrystallized from refluxing petroleum ether to give 1.86 g (8.8 mmol, 88%) of **17**. Colorless needles. M.p. 57–58°. $[\alpha]_D^{25} = +32.0$ ($c = 2.8$, MeOH). IR ($CHCl_3$): 2933, 1599, 1495, 1452, 1400, 1321, 1306, 1173, 1159, 1098, 1036, 712, 657, 566. ^{1}H-NMR (500 MHz, C_6D_6): 7.86–7.89 (*m*, 2 H); 6.72–6.76 (*m*, 2 H); 2.61 (*ddq*, $J = 6.9$, 5.6, 4.4, 1 H); 2.34 (*d*, $J = 6.9$, 1 H); 1.84 (*s*, 3 H); 1.37 (*d*, $J = 4.5$, 1 H); 0.76 (*d*, $J = 5.6$, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): 16.94; 21.48; 34.70; 35.80; 128.68; 129.98; 137.40; 144.11.

*(−)-(6S)-6-[(*p*-Tolylsulfonyl)amino]hept-1-ene.* a) *Formation of Di(but-2-enyl)magnesium*. A three-neck 100-ml round-bottom flask was outfitted with a reflux condenser, septum inlet, and a fritted tube (the other end of this tube was attached to a second three-necked flask equipped with a septum and gas inlet) and charged with Mg (0.98 g, 40 mmol) and 30 ml of dry Et_2O. After activation with a small amount of I_2 and with vigorous stirring, 4-bromobut-1-ene (3.5 ml, 34 mmol) was added *via* syringe pump over 25 min. After an additional 15 min of stirring, 1,4-dioxane (3.0 ml, 35 mmol) was added dropwise, resulting in a strong exothermic reaction and formation of a thick white precipitate. The mixture was stirred for 30 min, then the reaction mixture apparatus was tilted, and 5 psi Ar pressure was applied, forcing the soln. through the frit into the second flask to yield a clear light brown soln. The reaction flask, filtration apparatus, and solids were rinsed with an additional 15 ml of dry Et_2O, which was combined with the initial filtrate.

b) *Alkylation of Aziridine* **17**. A 250-ml round-bottom flask outfitted with a septum inlet and thermocouple was charged with CuI (1.13 g, 6.0 mmol) and 50 ml of Et_2O, the stirred slurry was cooled to $-70°$, and all of the above alkylmagnesium soln. was added slowly by syringe. The cooling bath was removed, and the soln. was allowed to warm slowly: at $-28°$ the color of the mixture changed from tan to deep orange, whence the cooling bath was replaced. When the temp. again reached $-70°$, **17** was added as its Et_2O soln. (1.8 g, 8.5 mmol in 10 ml) in one portion. The mixture was allowed to warm slowly to r.t. and then stirred for an additional 4 h, then it was quenched by the careful addition of 100 ml of a 4:1 (*v*/*v*) mixture of sat. aq. NH_4Cl and sat. aq. NH_4OH solns. This mixture was stirred vigorously under air for 2 h. The org. layer was then separated, and the aq. phase was extracted with Et_2O (4 × 50 ml). The combined org. fractions were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a clear colorless oil (2.3 g), which was purified by FC (25 mm × 6″ column, eluted with 20% (*v*/*v*) AcOEt/hexane) to give 2.14 g (8.0 mmol, 94%) of colorless oil. $[\alpha]_D^{25} = -16.4$ ($c = 3.6$, MeOH). IR (film): 2955, 2929, 2857, 1641, 1472, 1463, 1388, 1373, 1361, 1256, 1105, 1006, 954, 939, 910, 836, 811. ^{1}H-NMR (500 MHz, C_6D_6): 7.89–8.00 (*m*, 2 H); 6.85–6.92 (*m*, 2 H); 5.62 (*ddt*, *J* = 12.8, 8.4, 6.4, 1 H); 5.55 (*d*, *J* = 8.1, 1 H); 4.90–4.93 (*m*, 1 H); 4.89 (*t*, *J* = 2.8, 1 H); 3.28 (*sept.*, *J* = 6.9, 1 H); 1.93 (*s*, 3 H); 1.76–1.81 (*m*, 2 H); 1.10–1.35 (*m*, 4 H); 0.84 (*d*, *J* = 7.0). ^{13}C-NMR (101 MHz, C_6D_6): 21.50; 21.95; 25.46; 33.98; 37.32; 50.38; 115.03; 127.58; 130.07; 139.08; 139.98; 143.10.

*(+)-(6S)-6-({2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}(*p*-tolylsulfonyl)amino)hept-1-ene.* (−)-(6*S*)-6-[(*p*-Tolylsulfonyl)amino]hept-1-ene (2.0 g, 7.5 mmol) was added to a stirred slurry of NaH (215 mg, 9.0 mmol) in 40 ml of dry DMF at 0° by syringe pump over a period of 1 h. The mixture was stirred for an additional 50 min at 0° after addition was complete, then 2.14 g (9.0 mmol) of 1-bromo-2-[(*tert*-butyl)dimethylsiloxy]ethane was added dropwise. The mixture was allowed to warm to r.t. and stirred for 80 h. After addition of 40 ml of H_2O, the mixture was extracted with a 10% (*v*/*v*) mixture of Et_2O/pentane (5 × 50 ml). The combined org. extracts were dried (K_2CO_3), filtered, and concentrated *in vacuo* to afford 3.1 g of a yellow oil, which was purified by FC (25 mm × 6″ column, eluted with 8% (*v*/*v*) AcOEt/hexane) to give 2.8 g (6.7 mmol, 89%) of a clear, colorless oil. $[\alpha]_D^{25} = +14.3$ ($c = 2.2$, MeOH). IR (film): 3076, 2930, 2886, 2858, 1641, 1599, 1472, 1462, 1389, 1344, 1258, 1160, 1091, 1020, 1005, 911, 838, 815, 778, 715, 653. ^{1}H-NMR (500 MHz, C_6D_6): 7.75–7.72 (*m*, 2 H); 6.79–6.75 (*m*, 2 H); 5.68 (*ddt*, *J* = 17.1, 10.1, 6.7, 1 H); 4.98 (*dq*, *J* = 17.0, 1.7, 1 H); 4.96 (*ddt*, *J* = 10.1, 2.2, 1.2, 1 H); 4.09 (*td*, *J* = 9.6, 5.6, 1 H); 3.91 (*td*, *J* = 9.4, 5.7, 1 H); 3.89 (*sext.*, *J* = 6.7, 1 H); 3.28 (*ddd*, *J* = 14.8, 9.3, 5.6, 1 H); 3.12 (*ddd*, *J* = 14.8, 9.3, 5.7, 1 H); 1.94–1.89 (*m*, 2 H); 1.89 (*s*, 3 H); 1.32–1.18 (*m*, 3 H); 1.10–1.02 (*m*, 1 H); 0.99 (*s*, 9 H); 0.69 (*d*, *J* = 6.7, 3 H); 0.132 (*s*, 3 H); 0.124 (*s*, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): −4.68; 18.46; 21.43; 26.51; 34.08; 35.57; 45.42; 54.17; 64.36; 115.24; 127.88; 129.97; 138.99; 139.45; 142.92.

*(+)-(6S)-6-({[(*tert*-Butyl)dimethylsilyloxy]ethyl}amino)hept-1-ene.* a) *Formation of Sodium Naphthalide Soln.* To a stirred soln. of naphthalene (3.8 g, 30 mmol) in 30 ml of dry DME was added an excess of Na metal (*ca*. 1.3 g, 59 mmol). This mixture was stirred vigorously for 3 h at r.t. prior to use.

b) *Deprotection of* p-*Toluenesulfonate.* The sulfonamide (2.5 g, 5.9 mmol) was taken up in 50 ml of dry DME and cooled to $-74°$. The above naphthalide soln. was then added dropwise with vigorous stirring. Addition was continued until a persistent green color was achieved (*ca*. 12 ml). The mixture was allowed to warm to 0° and then quenched by addition of 5 ml of EtOH. The mixture was concentrated at reduced pressure to give a solid white residue, which was taken up in 30 ml of H_2O and extracted with Et_2O (4 × 25 ml). The combined org. extracts were rinsed with brine (25 ml), dried (K_2CO_3), filtered, and concentrated to give 4.2 g of an oily white solid, which was purified by FC (50 mm × 6″ column, eluted with 5% (*v*/*v*) AcOEt/hexane, followed by 20% AcOEt/hexane containing 2% Et_3N) to give 1.46 g (5.6 mmol, 96%) of a slightly yellow oil. $[\alpha]_D^{25} = +3.5$ ($c = 4.6$, MeOH). IR (film): 3077, 2955, 2929, 2857, 1822, 1641, 1472, 1463, 1388, 1373, 1361, 1256, 1105, 1006, 954, 939, 910, 836, 811, 777, 662. ^{1}H-NMR (500 MHz, C_6D_6): 5.78 (*ddt*, *J* = 17.1, 10.1, 6.7, 1 H); 5.04 (*dq*, *J* = 17.1, 1.7, 1 H); 4.99 (*ddt*, *J* = 10.1, 2.3, 1.2, 1 H); 3.65 (*t*, *J* = 5.38, 2 H); 2.71 (*dt*, *J* = 11.6, 5.3, 1 H); 2.62 (*dt*, *J* = 11.6, 5.5, 1 H); 2.55 (*sext.*, *J* = 6.1, 1 H); 2.00–1.95 (*m*, 2 H); 1.47 (br. *s*, 1 H); 1.44–1.35 (*m*, 3 H); 1.32

(*m*, 1 H); 1.00 (*d*, *J* = 6.8, 3 H); 0.97 (*s*, 9 H); 0.063 (*s*, 3 H); 0.061 (*s*, 3 H). ^{13}C-NMR (101 MHz, C_6D_6): 7.78; 18.87; 21.14; 25.94; 26.49; 34.74; 37.44; 49.96; 53.50; 63.63; 114.98; 139.49.

*(−)-(6*S*)-6-([(*tert*-Butoxy)carbonyl]{[2-(*tert*-butyl)dimethylsilyloxy]ethyl}amino)hept-1-ene* (**18**). To a stirred soln. of (+)-(6*S*)-6-({[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)hept-1-ene (1.3 g, 5.0 mmol) in THF (10 ml) was added di(*tert*-butyl) dicarbonate (1.2 g, 5.5 mmol). The soln. was stirred at r.t. for 10 h, then concentrated *in vacuo* and purified by FC (25 mm × 6″ column, eluted with 5% (*v*/*v*) AcOEt/hexane) to give 1.77 g (4.9 mmol, 98%) of a colorless oil. $[\alpha]_D^{25} = -1.3$ (*c* = 4.6, MeOH). IR (film): 3077, 2957, 2929, 2858, 1694, 1641, 1472, 1463, 1407, 1390, 1365, 1297, 1255, 1218, 1177, 1129, 1099, 1006, 996, 911, 837, 814, 776, 660. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 5.78 – 5.68 (*m*, 1 H); 5.06 – 4.94 (*m*, 1 H); 4.36 – 4.26 (*m*, 1 H); 3.81 – 3.70 (*m*, 2.5 H); 3.40 – 3.30 (*m*, 0.5 H); 3.31 – 3.20 (*m*, 1 H); 3.16 – 3.08 (*m*, 0.5 H); 2.02 – 1.88 (*m*, 2 H); 1.46 (*s*, 9 H); 1.46 – 1.39 (*m*, 1 H); 1.28 (*sext.*, *J* = 7.2, 2 H); 1.22 – 1.12 (*m*, 1 H); 1.02 – 0.96 (*m*, 3 H); 0.98 (*s*, 9 H); 0.102 (*s*, 3 H); 0.099 (*s*, 3 H).

*(−)-(5*Z*,10*S*)-10-([(*tert*-Butoxy)carbonyl]{2-[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)undec-5-enoic Acid* (**19**). a) *Formation of Ylide*. To a slurry of (4-carboxybutyl)triphenylphosphonium bromide (5.89 g, 13.3 mmol) in 20 ml of dry THF was added 26.5 ml of a 1.0M soln. of potassium salt of hexamethyldisilazane (KHMDS) in THF. The mixture was stirred vigorously for 1 h at r.t. After centrifugation, the clear, deep-orange ylide soln. was separated from the solids by syringe.

b) *Ozonolysis*/Wittig *Reaction*. A soln. of **18** (1.6 g, 4.4 mmol) in *t*-BuOMe was cooled to −76°; with vigorous stirring, a stream of O_3 in O_2 was bubbled through the soln. until a faint blue color was detected. The mixture was swept with Ar for 10 min to remove excess O_3 and O_2, and the above ylide soln. was then added dropwise. After warming to r.t., the mixture was stirred for an additional 2 h, and then quenched by the addition of 5 ml of H_2O. The mixture was washed with a 1:1 mixture of brine and 1N HCl (2 × 30 ml), and the aq. layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 3.9 g of a yellow oil, which was purified by FC (50 mm × 6″ column, eluted with 15% (*v*/*v*) AcOEt/hexane containing 1% of AcOH) to give 1.72 g (3.7 mmol, 84%) of **19**. Viscous, colorless oil. $[\alpha]_D^{25} = -3.4$ (*c* = 2.0, MeOH). ^{1}H-NMR (500 MHz, $(CD_3)_2CO$; mixture of conformers): 10.45 (br. *s*, 1 H); 5.45 – 5.34 (*m*, 2 H); 4.15 – 4.04 (*m*, 1 H); 3.92 – 3.83 (*m*, 0.5 H); 3.70 (*t*, 2 H); 3.22 – 3.15 (*m*, 1.5 H); 2.30 (*t*, *J* = 7.4, 2 H); 2.14 – 2.06 (*m*, 4 H); 1.65 (*quint.*, *J* = 7.4, 2 H); 1.61 – 1.50 (*m*, 1 H); 1.49 – 1.40 (*m*,1 H); 1.44 (*s*, 9 H); 1.38 – 1.24 (*m*, 2 H); 1.17 – 1.08 (*m*, 3 H); 0.91 (*s*, 9 H); 0.08 (*s*, 6 H).

*Benzyl (−)-(5*Z*,10*S*)-10-([(*tert*-Butoxy)carbonyl]{2-[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)undec-5-enoate*. To a stirred soln. of **19** (100 mg, 0.22 mmol), DMAP (29 mg, 0.24 mmol), and $PhCH_2OH$ (45 µl, 0.44 mmol) in CH_2Cl_2 (1.5 ml) was added 24 µl of a 1M CH_2Cl_2 soln. of DCC. The mixture was stirred at r.t. for 16 h, then concentrated, and purified by FC (15 mm × 6″ column, eluted with 5% (*v*/*v*) AcOEt/hexane) affording 114 mg (0.21 mmol, 95%) of a colorless oil. $[\alpha]_D^{25} = +0.63$ (*c* = 2.9, MeOH). IR (film): 2955, 2929, 2857, 1739, 1692, 1472, 1456, 1407, 1390, 1365, 1297, 1254, 1216, 1172, 1099, 1005, 931, 837, 777, 697. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 7.24 – 7.20 (*m*, 1 H); 7.14 – 7.05 (*m*, 4 H); 5.41 – 5.23 (*m*, 2 H); 5.02 (*s*, 2 H); 4.38 – 4.26 (*m*, 0.5 H); 3.96 – 3.72 (*m*,2.5 H); 3.43 – 3.12 (*m*, 2 H); 2.15 (*t*, 3 H); 1.96 (*quint.*, *J* = 7.5, 4 H); 1.63 (*quint.*, *J* = 7.5, 2 H); 1.52 – 1.41 (*m*, 1 H); 1.47 (*s*, 9 H); 1.33 – 1.16 (*m*, 3 H); 1.05 – 0.98 (*m*, 3 H); 0.109 (*s*, 3 H); 0.106 (*s*, 3 H); 0.98 (*s*, 9 H).

*Benzyl (−)-(5*Z*,10*S*)-10-{[(*tert*-Butoxy)carbonyl](2-hydroxyethyl)amino}undec-5-enoate* (**20**). To a stirred soln. of benzyl undec-5-enoate described above (100 mg, 0.18 mmol) in 1 ml of THF was added 0.2 ml of a 1M THF soln. of Bu_4NF. The mixture was stirred at r.t. for 16 h, then concentrated and purified by FC (11 mm × 6″ column, eluted with 20% (*v*/*v*) AcOEt/hexane) to yield 76 mg (0.17 mmol, 97%) of **20**. Colorless oil. $[\alpha]_D^{25} = -3.30$ (*c* = 1.6, MeOH). IR (film): 3077, 2957, 2929, 2858, 1694, 1641, 1472, 1463, 1407, 1390, 1365, 1297, 1255, 1218, 1177, 1129, 1099, 1006, 996, 911, 837, 814, 776, 660. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 7.23 – 7.20 (*m*, 1 H); 7.13 – 6.98 (*m*, 4 H); 5.39 – 5.33 (*m*, 1 H); 5.32 – 5.26 (*m*, 1 H); 5.01 (*s*, 2 H); 3.85 – 3.78 (*m*, 0.5 H); 3.76 – 3.50 (*m*, 2.5 H); 3.21 – 3.00 (*m*, 2 H); 2.15 (*t*, 2 H); 2.01 – 1.90 (*m*, 4 H); 1.63 (*quint.*, *J* = 7.3, 2 H); 1.42 (*s*, 9 H); 1.31 – 1.20 (*m*, 3 H); 1.16 – 1.05 (*m*, 1 H); 0.93 – 0.82 (*m*, 3 H).

*Benzyl (5*Z*,10*S*)-10-([(*tert*-Butoxy)carbonyl]{2-[(5*Z*,10*S*)-10-([(*tert*-butoxy)carbonyl]{2-[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)undec-5-enoyloxy]ethyl}amino)undec-5-enoate* (**21**). To a stirred CH_2Cl_2 (0.5 ml) soln. of **20** (50 mg, 0.12 mmol), DMAP (17 mg, 0.14 mmol), and DCC (130 µl of a 1M CH_2Cl_2 soln.) was added **19** as its CH_2Cl_2 soln. (53 mg, 0.12 mmol, in 500 µl). The mixture was stirred at r.t. for 4 h, and then placed directly on a FC column (11 mm × 6″), which was eluted with 15% (*v*/*v*) AcOEt/hexane to give 79 mg (0.09 mmol, 78% yield) of **21**. Colorless, viscous oil. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 7.23 – 7.20 (*m*, 1 H); 7.13 – 6.98 (*m*, 4 H); 5.51 – 5.26 (*m*, 4 H); 5.02 (*s*, 2 H); 3.98 – 3.67 (*m*, 4 H); 3.57 – 3.01 (*m*, 6 H); 2.30 – 2.00 (*m*, 8 H); 1.78 – 1.51 (*m*, 6 H); 1.50 – 1.48 (br. *s*, 18 H); 1.38 – 1.21 (*m*, 10 H); 1.05 – 0.96 (*m*, 15 H); 0.08 (*s*, 6 H).

*'Trimeric' Ester Benzyl (5Z,10S)-10-([(*tert*-Butoxy)carbonyl]{2-[(5Z,10S)-10-([(*tert*-butoxy)carbonyl]{2-[(5Z,10S)-10-([(*tert*-butoxy)carbonyl]{2-[(*tert*-butyl)dimethylsilyloxy]ethyl}amino)undec-5-enoyloxy]ethyl}-amino]undec-5-enoyloxy]ethyl}aminoundec-5-enoate.* To a stirred soln. of **21** in THF (79 mg, 0.09 mmol, in 0.4 ml) was added 0.1 ml of a 1M THF soln. of Bu_4NF. The mixture was stirred for 3 h and then concentrated.The residue was placed on a FC column (11 mm × 6″), which was eluted with 30% (*v*/*v*) AcOEt/hexane to give 63 mg (83 μmol) of the alcohol corresponding to **21** as a colorless oil. This was taken up in 0.5 ml CH_2Cl_2, to which were added DMAP (12 mg, 98μmol), DCC (87 μl, of a 1M CH_2Cl_2 soln.), and carboxylic acid **19** (40 mg, 87 μmol). The mixture was stirred at r.t. for 6 h, then placed directly on a FC column, 11 mm × 6″ and eluted with 20% (*v*/*v*) AcOEt/hexane to give 90 mg (0.075 mmol, 83% yield based on **21**) of a colorless oil. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 7.23–7.20 (*m*, 1 H); 7.13–6.98 (*m*, 4 H); 5.51–5.26 (*m*, 4 H); 5.02 (*s*, 2 H); 3.98–3.67 (*m*, 4 H); 3.57–3.01 (*m*, 6 H); 2.30–2.00 (*m*, 8 H); 1.78–1.51 (*m*, 6 H); 1.50–1.48 (br. *s*, 18 H); 1.38–1.21 (*m*, 10 H); 1.05–0.96 (*m*, 15 H); 0.08 (*s*, 6 H). EI-MS (positive ion): 998.4 (13, $[M-2(\text{Boc})+H]^+$), 999.4 (9), 1098.4 (30, $[M-\text{Boc}+H]^+$), 1099.4 (20), 1100.4 (9), 1198.4 (4, $[M+H]^+$), 1220.4 (100, $[M+Na]^+$), 1221.4 (73), 1222.4 (31), 1252.4 (18, $[M+K]^+$), 1253.4 (15), 1254.3 (8).

*(10S)-10-{[(*tert*-Butoxy)carbonyl][2-((10S)-10-{[(*tert*-butoxy)carbonyl][2-((10S)-10-{[(*tert*-butoxy)carbonyl](2-hydroxyethyl)amino}undecanoyloxy)ethyl]amino}undecanoyloxy)ethyl]amino}undecanoic Acid* (**22**). A soln. of the 'trimeric' benzyl ester (see above) (78 mg, 0.065 mmol) in THF (1.0 ml) was treated with Bu_4NF (70 μl, of a 1M THF soln.) and stirred at r.t. for 3 h. The mixture was concentrated and placed on a FC column (11 mm × 6″), which was eluted with 30% (*v*/*v*) AcOEt/hexane to give 59 mg of the alcohol corresponding to the 'trimeric' benzyl ester as a colorless oil. This oil was taken up in MeOH to which 5 mg of 5% Pd/C powder was added. The mixture was stirred vigorously under 15 psi H_2 for 8 h, then filtered through a 0.22 μ *Teflon* syringe-tip filter, and concentrated *in vacuo* to give 57 mg of a colorless oil, which was used as-is without further purification (57 μmol, 88% yield from 'trimeric' benzyl ester). ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 4.48–4.24 (*m*, 5 H); 3.94–3.58 (*m*, 3.5 H); 3.52–2.96 (*m*, 6.5 H); 2.26–2.16 (*m*, 6 H); 1.68–1.54 (*m*, 6 H); 1.48 (br. *s*, 18 H); 1.43 (br. *s*, 9 H); 1.32–1.14 (*m*, 34 H); 1.06–1.02 (*m*, 9 H).

*4,18,32-Tris[(*tert*-butoxy)carbonyl]-5,19,33-trimethyl-1,15,29-trioxa-4,18,32-triazacyclodotetracontane-14,28,42-trione* (N,N′,N″-*Tris-Boc-PAML681*). To a refluxing soln. of 2-chloro-1-methylpyridinium iodide (36 mg, 140 μmol) in 100 ml of MeCN was added a MeCN (5 ml) soln. of 'trimeric' ω-hydroxy acid **22**, containing 40 μl (280 μmol) of Et_3N, over a period of 3 h. Reflux was continued for 30 min after addition was complete. The mixture was then concentrated *in vacuo*, taken up in 3 ml of H_2O, and extracted with Et_2O (5 × 3 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 55 mg of a yellow residue, which was purified by FC (11 mm × 4.5″ column, eluted with 20% (*v*/*v*) AcOEt/hexane) to give 24.0 mg (24.5 μmol, 70% yield) of a colorless oil. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 4.44–4.24 (*m*, 7.5 H); 3.90–3.78 (br. *s*, 1.5 H); 3.48–3.32 (br. *s*, 3 H); 3.32–2.94 (*m*, 3 H); 2.24–2.15 (br. *s*, 6 H); 1.66–1.56 (*m*, 6 H); 1.54–1.48 (*m*, 3 H); 1.47 (br. *s*, 27 H); 1.43 (br. *s*, 9 H); 1.32–1.14 (*m*, 33 H); 1.1 (*d*, *J* = 7.2, 9 H). ES-MS (positive ion): 514 (52, $[M+2\,Na]^{2+}$), 515 (26), 522 (4, $[M+Na+K]^{2+}$), 521 (2), 1004 (100, $[M+Na]^+$), 1005 (72), 1004 (31), 1020 (12, $[M+K]^+$), 1021 (9), 1023 (4).

5,19,33-Trimethyl-1,15,29-trioxa-4,18,32-triazacyclodotetracontane-14,28,42-trione (PAML681; **23**). A 1.0 mg (1.0 μmol) sample of *N,N′,N″*-tris-Boc-PAML681 was taken up in neat CF_3COOH (50 μl) and allowed to sit at 40° for 12 h. The excess acid was evaporated at reduced pressure, then 1 ml of Et_2O and 100 μl of 20% aq. K_2CO_3 were added. After vigorous mixing, the org. layer was separated and the aq. layer extracted with Et_2O (3 × 0.5 ml). The combined org. fractions were filtered through a plug of anh. K_2CO_3 and concentrated to give 0.6 mg (0.99 μmol, 99% yield) of pure **23**. $[\alpha]_D^{25} = +7.98$ ($c = 2.9$, CH_2Cl_2). IR (film): 2928, 2854, 1736, 1464, 1420, 1374, 1242, 1166, 1114, 1060, 1024, 724. ^{1}H-NMR (500 MHz, C_6D_6): 4.20 (*ddd*, *J* = 11.1, 6.8, 4.3, 3 H); 4.14 (*ddd*, *J* = 11.1, 6.8, 4.4, 3 H); 2.72 (*ddd*, *J* = 12.7, 6.3, 4.3, 3 H); 2.63 (*ddd*, *J* = 12.7, 6.8, 4.4, 3 H); 2.56–2.49 (*m*, 3 H); 2.20 (*t*, *J* = 7.4, 6 H); 1.63 (*quint.*, *J* = 7.1, 6 H); 1.41–1.19 (*m*, 36 H); 0.97 (*d*, *J* = 6.4, 9 H). ^{13}C-NMR (126 MHz, C_6D_6): 173.1 (C(1)); 64.4 (OCH_2CH_2N); 52.9 (C(10)); 45.9 (OCH_2CH_2N); 37.5 (C(9)); 34.3 (C(2)); 30.0; 29.7; 29.45; 29.3 (C(4)); 26.1 (C(8)); 25.3 (C(3)); 20.7 (C(11)). ESI-MS (positive ion): 228 (70, $[M+3\,H]^{3+}$), 342 (100, $[M+2\,H]^{2+}$), 682 (32, $[M+H]^+$), 721 (5, $[M+K]^+$). HR-MS (ESI): 682.5722 ($C_{39}H_{76}N_3O_6^+$; calc. 682.5734).

The synthetic procedure for PAML-1362 (hexamer) given below is representative of the process used for the production of all the PAMLs listed in *Scheme 4*.

Saturated Open-Chain Hexameric ω-Hydroxy Acid. A mixture of the 'trimeric' ester (18 mg, 15 μmol; see above) and 1 mg 5% Pd/C in 0.5 ml of dry MeOH was stirred under 15 psi H_2 gas for 14 h. The mixture was filtered through a 0.22 μ syringe-tip filter and concentrated *in vacuo* to give 17 mg of a colorless oil. This was taken in 0.3 ml CH_2Cl_2, to which were added DMAP (5 mg, 40 μmol), DCC (27 μl of 1M CH_2Cl_2 soln.), and the

alcohol corresponding to the trimeric ester (16 mg, 15 μmol). After stirring for 12 h, this mixture was placed directly on a FC column and eluted with 25% (*v*/*v*) AcOEt/hexane to afford 28 mg of the hexameric ester (13 μmol, 85% yield based on **21**). This material was dissolved in THF and treated with Bu_4NF (16 μl of 1M THF soln.), and stirred at r.t. for 2 h. The mixture was placed directly on a FC column (11 mm × 4.5″) and eluted with 50% (*v*/*v*) AcOEt/hexane) to afford 26 mg of the corresponding alcohol as a colorless oil. Concurrent hydrogenolysis of the benzyl ester and hydrogenation of the C=C bonds was affected in 0.5 ml MeOH with 1 mg of 5% Pd/C under 15 psi H_2 gas for 15 h. Subsequently, the mixture was forced through a 0.22 μ syringe-tip filter and concentrated *in vacuo* to give 23 mg (12 μmol, 79% yield based on **23**) of a colorless oil, which was used for the next reaction without further purification. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 4.47–4.24 (*m*, 10 H); 3.95–3.62 (*m*, 7 H); 3.54–3.16 (*m*, 13 H); 2.26–2.17 (*m*, 12 H); 1.68–1.56 (*m*, 12 H); 1.48 (br. *s*, 36 H); 1.44 (br. *s*, 18 H); 1.32–1.14 (*m*, 68 H); 1.06–1.02 (*m*, 18 H).

Per-N-*Boc-PAML1-362* (*Macrolactonization of Cyclic Hexamer*). To a refluxing soln. of 2-chloro-1-methylpyridinium iodide (5.1 mg, 20 μmol) in 20 ml of MeCN was added a MeCN (2 ml) soln. of hexameric ω-hydroxy acid (18 mg, 9.1 μmol), which contains 5 μl (35 μmol) of Et_3N, over a period of 3 h. Reflux was continued for 30 min after addition was complete. The mixture was then concentrated *in vacuo*, taken up in 1 ml of H_2O, and extracted with Et_2O (5 × 1 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 21 mg of a yellow residue. Purification by FC (11 mm × 4″ column eluted with 35% (*v*/*v*) AcOEt/hexane) gave 10 mg (5.1 μmol, 56% yield) of per-*N*-Boc-PAML-1362. ^{1}H-NMR (500 MHz, C_6D_6; mixture of conformers): 4.44–4.24 (*m*, 15 H); 3.90–3.78 (br. *s*, 3 H); 3.46–3.30 (br. *s*, 6 H); 3.29–2.95 (*m*, 6 H); 2.24–2.16 (br. *s*, 12 H); 1.66–1.57 (*m*, 12 H); 1.54–1.48 (*m*, 6 H); 1.48 (br. *s*, 54 H); 1.44 (br. *s*, 18 H); 1.32–1.13 (*m*, 66 H); 1.12 (*d*, J = 7.2, 18 H).

PAML-1362. By a procedure analogous to that described above for the deprotection of PAML-681, 8.8 mg of *N*,*N*,*N*,*N*,*N*,*N*-Boc_6-PAML-1362 was treated with CF_3COOH to afford 5.1 mg of a colorless residue (4.0 μmol, 89%). $[\alpha]_D^{25} = +8.1$ (c = 0.5, CH_2Cl_2). IR (film): 2928, 2854, 1736, 1464, 1420, 1374, 1242, 1166, 1114, 1060, 1024, 724. ^{1}H-NMR (500 MHz, C_6D_6): 4.20 (*ddd*, J = 11.1, 6.8, 4.3, 6 H); 4.14 (*ddd*, J = 11.1, 6.8, 4.4, 6 H); 2.72 (*ddd*, J = 12.7, 6.3, 4.3, 6 H); 2.63 (*ddd*, J = 12.7, 6.8, 4.4, 6 H); 2.56–2.49 (*m*, 6 H); 2.20 (*t*, J = 7.4, 12 H); 1.63 (*quint.*, J = 7.1, 12 H); 1.41–1.19 (*m*, 72 H); 0.97 (*d*, J = 6.4, 18 H). ^{13}C-NMR (126 MHz, C_6D_6): 173.0 (C(1)); 64.5 (OCH_2CH_2N); 53.1 (C(10)); 46.0 (OCH_2CH_2N); 37.6 (C(9)); 34.4 (C(2)); 30.2; 29.9; 29.7; 29.5; 26.2; 25.4 (C(3)); 20.7 (C(11)). ES-MS (positive ion): 228 (34, $[M+6H]^{6+}$), 342 (42, $[M+4H]^{4+}$), 455 (100, $[M+3H]^{3+}$), 682 (50, $[M+2H]^{2+}$), 1362 (12, $[M+H]^{+}$).

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