Synthesis and Ring Contraction Reactions of Polyazamacrolides

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The synthesis of three analogues of the single most abundant component of a ladybird beetle (*Epilachna borealis*) defensive secretion, the trimeric 42-membered polyazamacrolide PAML 681, is described. Construction of the nonnatural macrocyclic trimers began with the preparation of the corresponding monomeric segments, followed by their oligomerization and a final macrolactonization step of the activated linear trimeric hydroxy acid. The relative rates of the *O*-to-*N* acyl migrations that are characteristic of PAML 681 itself, as well as of the synthetic analogues, were investigated. These studies showed that changes in the substitution pattern adjacent to the nucleophilic nitrogen atom, along with changes in the size of the oxaazacyclic intermediates, have substantial effects on the polyazamacrolide rearrangement rates.

Introduction

Studies of the chemical ecology of insects and related arthropods reveal that these enormously diverse and successful animals exploit a wide range of molecular structures for defensive and communicative purposes.[1] It can be anticipated that chemical defenses should be particularly important in preadult life stages, and this expectation has recently been confirmed in the case of the pupae of several species of coccinellid (ladybird) beetles. These pupae are defended by a new class of alkaloids, the azamacrolides and their oligomeric cousins, the polyazamacrolides, which constitute a structurally unprecedented addition to the already rich array of insect defensive chemicals. Among the first of these macrocycles to be characterized were epilachnene (**1**) and epilachnadiene (**2**) (Figure 1), from the pupal defensive secretion of the Mexican bean beetle (*Epilachna varivestis*).[2]

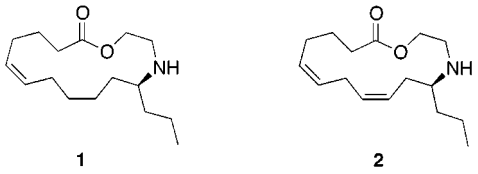

Figure 1.

Epilachnenic and epilachnadienic acids (**3** and **4**) (Figure 2), the hydroxyethylamino acids from which these 15-membered lactones are derived, were subsequently found to form three dimeric, 30-membered lactonic alkaloids (**5**, **6**, and **7**), which are the major components of the exudate of another coccinellid pupa, that of *Subcoccinella 24-punctata*.[3]

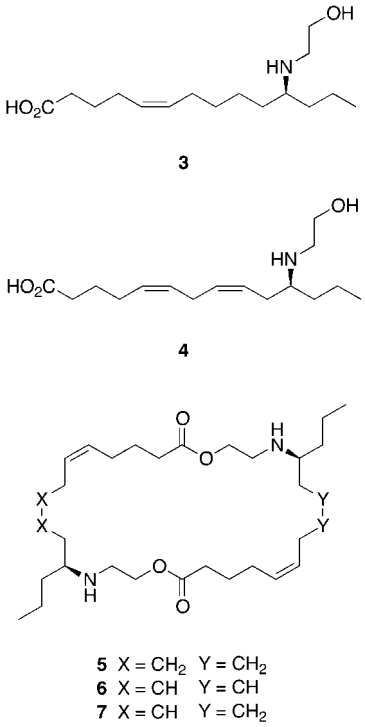

Figure 2.

Three closely related, saturated (*ω*-1)-hydroxyethylamino acids (**8**, **9** and **10**) (Figure 3) provide the building blocks for a combinatorial library of over a thousand polyazamacrolides (PAMLs) deployed by pupae of still another ladybird, the squash beetle *Epilachna borealis*. The random incorporation of these three acids into a series of oligomeric lactones, consisting chiefly of trimers, tetramers, and pentamers but including everything from dimers to at least heptamers, gives rise to the most complex arthropod defensive secretion ever characterized.[4a,b]

A striking feature of the chemistry of PAMLs is their tendency to undergo multiple intramolecular acyl group

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(1) Meinwald, J.; Eisner, T. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12.

(2) King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105. Attygalle, A. B.; McCormick, K. D.; Blankespoor, C. L.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5204. Attygalle, A. B.; Smedley, S.; Eisner, T.; Meinwald, J. *Experientia* **1996**, *52*, 616.

(3) (a) Schröder, F.; Smedley, S.; Gibbons, L. K.; Farmer, J.; Attygalle, A.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13387. (b) Gronquist, M. R.; Meinwald, J. *J. Org. Chem.* **2000**, *2*, 1075.

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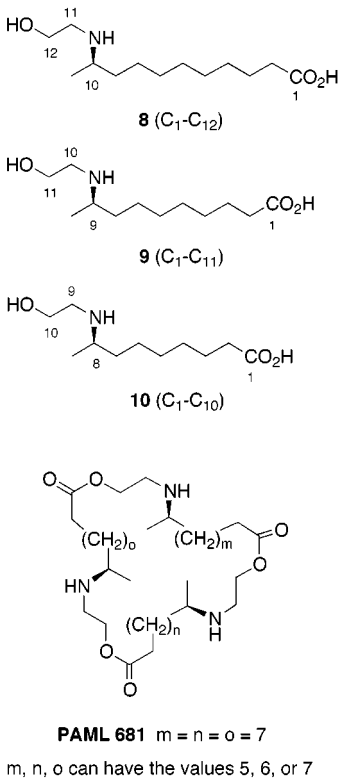


Figure 3.

migrations. This phenomena is, of course, not unique to these alkaloids; it has been observed in a variety of natural products, including the *Solanum* alkaloids,[5] adenosine peptidyl derivatives,[6] the immunosuppressant drug cyclosporin A, and other peptides containing β-hydroxyl residues.[7] This type of rearrangement also provides a useful strategy for the convergent synthesis of peptides,[8a,b] peptidomimetic structures,[8c] proteins,[8d] and macrocyclic lactones.[9] In the case of the PAMLs, each of these *O*-to-*N* acyl migration steps results in the reduction of the ring size of the macrocycle by three members; a basic nitrogen atom is converted into a neutral amide nitrogen atom, and a primary hydroxyl group is exposed (Figure 4).

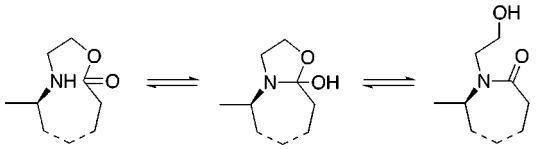


Figure 4.

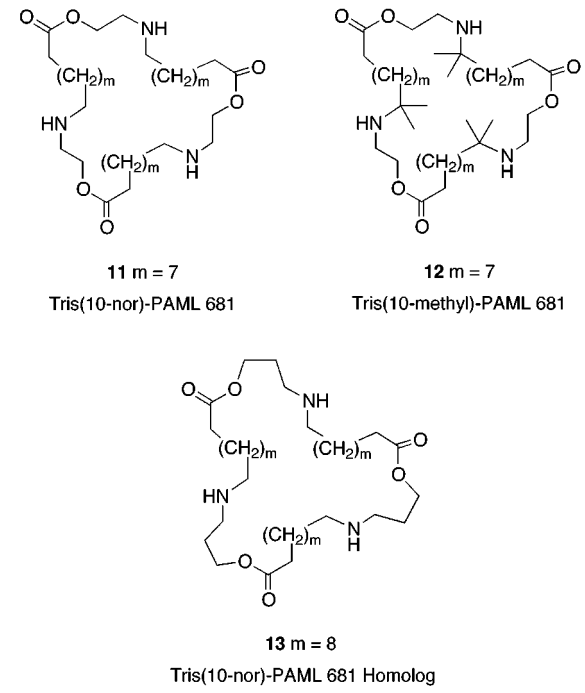


Figure 5.

The large number of additional structures that this pathway generates contributes greatly to the structural diversity of this ladybird's pupal exudate. In each of these natural products, the nitrogen atom is able to initiate an *O*-to-*N* acyl group transfer via a five-membered ring intermediate. In addition, there is always a single alkyl group on the carbon atom adjacent to the nitrogen atom. There is no information on whether these particular structural features are important for the biological functioning of these compounds as insect repellents. We have consequently become interested in exploring the chemistry of some nonnatural polyazamacrolides, which differ from the natural products (a) in the degree of alkyl group substitution at the carbon adjacent to the basic nitrogen and (b) in the distance between the nucleophilic nitrogen atom and the nearest lactonic carbonyl group. With these objectives in mind, we have undertaken syntheses of three analogues of the single most abundant component of the *E. borealis* secretion, the trimeric, 42-membered PAML 681. We here report the synthesis of a small set of nonnatural polyazamacrolides, as well as studies of their *O*-to-*N* acyl group migration. The specific target compounds we selected were a trisnor lactone (**11**), a trismethyl lactone (**12**), and a trishomo lactone (**13**) (Figure 5). These compounds allow us to study the influence of the methyl substitution adjacent to the nucleophilic nitrogen, along with the importance of the size of the intermediate ring (five- or six-membered) in the PAMLs' contraction process.

(4) (a) Schröder, F.; Farmer, J.; Attygalle, A.; Smedley, S.; Eisner, T.; Meinwald, J. *Science* **1998**, *281*, 428. (b) Schröder, F.; Farmer, J.; Smedley, S.; Attygalle, A.; Eisner, T.; Meinwald, J. *J. Am. Chem. Soc.* **2000**, *122*, 3628. (c) Farmer, J.; Attygalle, A.; Smedley, S.; Eisner, T.; Meinwald, J. *Tetrahedron Lett.* **1997**, *38*, 2787. (d) Farmer, J.; Schröder, F.; Meinwald, J. *Helv. Chim. Acta* **2000**, *83*, 2594.

(5) Adam, G.; Schreiber, K. *Chem. Ber.* **1966**, *99*, 3173.

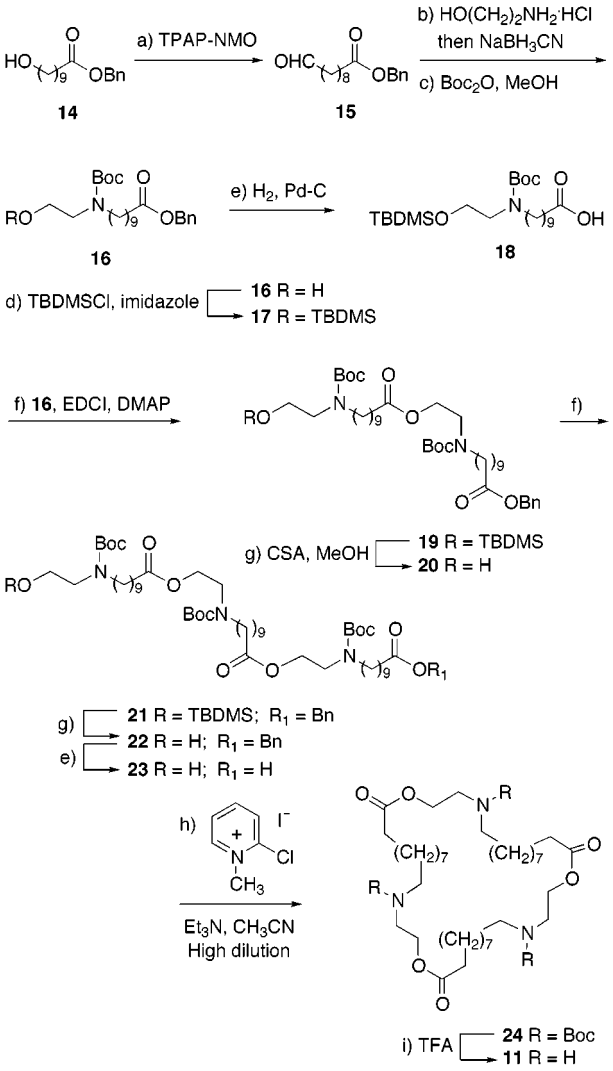
(6) Neumann, H.; Shashoua, V. E.; Sheehan, J. C.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1968**, *61*, 1207.

(7) (a) Pohl, E.; Sheldrick, G. M.; Bölsterli, J. J.; Kallen, J.; Traber, R.; Walkinshaw, M. D. *Helv. Chim. Acta* **1996**, *79*, 1635. Oliyai, R.; Safadi, M.; Meier, P. G.; Hu, M. K.; Rich, D. H.; Stella, V. J. *Int. J. Peptide Protein Res.* **1994**, *43*, 239. Rüegger, A.; Kuhn, M.; Lichti, H.; Loosli, H. R.; Hugenin, R.; Quiquerez, C.; von Wartburg, A. *Helv. Chim. Acta* **1976**, *59*, 1075. (b) Oliyai, R.; Stella, V. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2735.

(8) (a) For a recent review, see: Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449. See also: Offer, J.; Dawson, P. E. *Org. Lett.* **2000**, *2*, 23. Tam, J. P.; Lu, Y.-A.; Yu, Q. *J. Am. Chem. Soc.* **1999**, *121*, 4316 and references therein. (b) Kemp, D. S. *Biopolymers* **1981**, *20*, 1793. Kemp, D. S.; Kerkman, D. J.; Leung, S. L.; Hanson, G. *J. Org. Chem.* **1981**, *46*, 490. Kemp, D. S.; Vellaccio, F. *J. Org. Chem.* **1975**, *40*, 3464. Sakakibara, S.; Shin, K. H.; Hess, G. P. *J. Am. Chem. Soc.* **1962**, *84*, 4921. (c) Derrer, S.; Feeder, N.; Teat, S. J.; Davies, J. E.; Holmes, A. B. *Tetrahedron Lett.* **1998**, *39*, 9309. (d) Camarero, J. A.; Muir, T. W. *J. Am. Chem. Soc.* **1999**, *121*, 5597 and references therein.

(9) Gribble, G. W.; Silva, R. A. *Tetrahedron Lett.* **1996**, *37*, 2145.

Scheme 1



Results and Discussion

Synthesis of Tris(10-nor)PAML 681 (11). Construction of the first nonnatural macrocyclic trimer **11** required the preparation of the corresponding monomeric segment (C1−C12, **16**), differing from the natural building block **8** by the absence of a methyl substituent at C10, followed by subsequent assembly and cyclization of the activated open chain trimer **23** (Scheme 1). Benzyl 10-hydroxydecanoate **14**[10] was smoothly oxidized with TPAP/NMO[11] to the aldehyde **15** in 81% yield. Formation of the monomeric protected amino alcohol **16** was achieved by reductive amination of **15** with ethanolamine hydrochloride in the presence of $NaBH_3CN$, followed by acylation of the amine with Boc_2O[12] (48% yield, two steps). To obtain the dimeric unit **19**, alcohol **16** was conveniently transformed into acid **18**, which was then coupled with another equivalent of alcohol **16** using an 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI)-mediated procedure.[13] After considerable experimentation, optimal results were obtained when monomers **16** and **18** were combined at room temperature by treatment with the water-soluble carbodiimide and DMAP as catalyst. Alternative coupling reagents (bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl)[14] or 2,4,6-trichlorobenzoyl chloride[15]) gave far lower yields, while DCC[16] complicated the product purification. It is interesting to note that performing the chemoselective acid-catalyzed TBDMS ether desilylation (camphorsulfonic acid (CSA), CH_2Cl_2/MeOH, 0 °C)[17a] was found to be capricious depending upon reaction conditions: longer times and/or higher temperatures afforded mixtures resulting from partial amine deprotection.[17b] Reiteration of the desilylation/coupling protocol starting with dimer **19** led to open chain trimer **21**, which was converted to hydroxy acid **23** after removal of the benzyl and TBDMS protecting groups. Overall, activated trimer **23** was prepared from monomeric precursor **16** in seven steps and 56% yield. Finally, subjection of hydroxy acid **23** to Mukaiyama's reagent promoted lactonization[18] under high dilution conditions ($\sim 3 \times 10^{-4}$ M) in refluxing acetonitrile resulted in cyclization, providing the *N*-Boc-protected macrocycle **24**, which was treated with neat TFA to afford the desired 42-membered polyazamacrolide **11** in 60% yield for the two steps. Examination of the ^1H, ^{13}C, and 2D NMR (COSY and HMQC) spectra of cyclic trimer **24** showed that upon macrocyclization, only a single set of ^1H and ^{13}C resonances, corresponding to a mixture of rotamers of the monomeric subunits,[19] was observable. In addition, the unequivocal identification of polyazamacrolide **11** was supported on the basis of its LC-electrospray ionization mass spectrometric (ESIMS) analysis, which indicated its chromatographic homogeneity in different eluent solvent mixtures and showed the expected MS pattern: operating in positive ion electrospray mode, trisnor lactone **11** produced multiple charged ions with up to three charges corresponding to the number of basic nitrogen atoms present in the molecule [*m*/*z* 641 $(M+H)^+$, 321 $(M+2H)^{2+}$, 214 $(M+3H)^{3+}$)].

Synthesis of Tris(10-methyl)PAML 681 (12). The PAML 681 analogue bearing *gem*-dimethyl substituents vicinal to each of the nitrogen atoms was prepared to evaluate the influence of the additional methyl group on the chemical and functional behavior of PAML 681. The approach implemented for the construction of **12** (Scheme 2) relies on the strategy described in the previously reported synthesis of natural PAML 681.[4a] Thus, opening of the activated 2,2-dimethyltosylaziridine **25**[20] with

(10) Flippin, L. A.; Gallagher, D. W.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 1430. Holt, A. D.; Luengo, J. I.; Yamashita, D. S.; Oh, H.-J.; Konialian, A. L.; Yen, H.-K.; Rozamus, L. W.; Brandt, M.; Bossard, M. J.; Levy, M. A.; Eggleston, D. S.; Liang, J.; Schultz, L. W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 9925.

(11) Ley, S. V.; Norman, J.; Griffith, W. P.; Mardsen, S. P. *Synthesis* **1994**, 639.

(12) For the recent application and discussion of protecting group tuning techniques to chemoenzymatic synthesis of polyazamacrolides, see: Lu, W.; Sih, C. J. *Tetrahedron Lett.* **1999**, *40*, 4965. See also: Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213.

(13) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962.

(14) Balleste-Rodes, M.; Palomo-Coll, A. L. *Synth. Commun.* **1984**, *14*, 515.

(15) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(16) Ramage, R.; MacLeod, A. M.; Rose, G. W. *Tetrahedron* **1991**, *47*, 5625. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *46*, 4475.

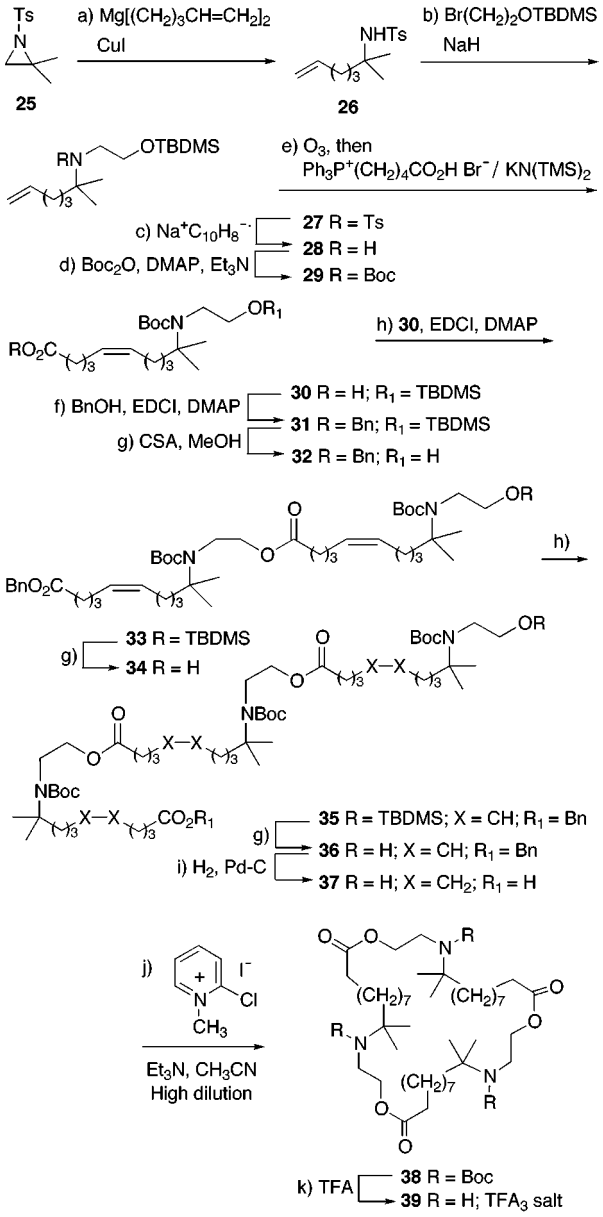
(17) (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031. (b) Deprotection of *N*-Boc protected amines is usually achieved by using strong acids (TFA, HCl, H_2SO_4, *p*-toluenesulfonic acid, methanesulfonic acid) at room temperature: Greene, T. W.; Wuts, P. G.-M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999; Chapter 7, p 518.

(18) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

(19) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771.

(20) Alul, R.; Cleaver, M. B.; Taylor, J.-S. *Inorg. Chem.* **1992**, *31*, 3636.

Scheme 2



magnesium bis(3-butenyl) copper reagent[21] was accomplished with excellent regioselectivity to afford tosyl amide **26**; the exclusive presence of the desired single regioisomer was shown by ^{1}H NMR examination of unpurified reaction products. The slightly lower yields compared to those obtained for the α-monomethylamino derivative[4a] are easily rationalized on the basis of increased steric hindrance, since nucleophilic attack to electronically deficient aziridines is known to involve an S_N2-type mechanism.[22] Subsequent alkylation of **26** (NaH/*tert*-(butyldimethylsilyloxy)ethyl bromide, DMF, 0 °C) led to silyl ether **27** (72% yield, two steps). Following tosyl group removal,[23] conversion of amine **28** into its *N*-Boc derivative required long reaction times and catalytic amounts of DMAP, manifesting the low reactivity of the hindered neopentyl nitrogen atom.[24] After protecting group exchange, ozonolysis of carbamate **29** under carefully controlled reaction conditions followed by immediate Wittig olefination of the crude ozonide[25] with 4-carboxybutyltriphenylphosphonium ylide provided unsaturated monomer **30** in 94% overall yield from **29**. In accordance with expectations for a nonstabilized ylide, a *cis* configuration of the double bond for unsaturated carbamate **29** was observed on the basis of the absence of large *trans* ^{1}H,^{1}H coupling constants for the olefinic protons (2H at δ 5.29−5.45, 2m). Additional benzylation of acid **30** (BnOH/EDCI/DMAP, CH_2Cl_2, rt)[26] and TBDMS ether cleavage with CSA gave monoprotected **32**, which was coupled with its monomeric partner **30** to afford dimer **33** in 90% yield. Desilylation of dimer **33**, followed by chain elongation and deprotection, afforded alcohol **36** in up to 54% yield. Simultaneous hydrogenation−debenzylation of **36** gave long chain hydroxy acid **37**, which was converted to cyclic trimer **38** after macrolactonization in the presence of Mukaiyama's reagent. In comparing the ^{1}H and ^{13}C NMR data of *N*-Boc-protected polyazamacrolide **38** with the data previously observed for the trisnor analogue **24**, disappearance of carbamate rotamers was evident. This difference is most likely due to severe steric interaction between the *gem*-dimethyl substituents and the *tert*-butoxycarbonyl protecting group.[27] Finally, carbamate deprotection allowed the isolation of tris(10-methyl)PAML 681 (**12**) as its tris(trifluoroacetate) **39** (8% overall yield, 14 steps), which displayed NMR and MS characteristics consistent with the desired macrocyclic structure. As a consequence of the unexpectedly high rates for the *O*-to-*N* acyl migration of the corresponding free amine **12**, deprotonation of tris(10-methyl)PAML 681 tris(trifluoroacetate) was deferred until performance of the rearrangement rate studies (vide infra).

Synthesis of Tris(10-nor)PAML 681 Homologue (13). To provide a model for exploring the chemistry of PAMLs analogues with an additional carbon atom between the nitrogen and the nearest carbonyl group, we prepared the PAML homologue **13** starting from commercially available 11-aminodecanoic acid as outlined in Scheme 3. The reaction sequence was initiated by Michael addition of sodium 11-aminodecanoate to methyl acrylate, followed by protection of the resulting secondary amine as its Boc derivative to furnish hemi ester **40** in a one-pot procedure and 77% yield. Chemoselective reduction of **40** with $LiBH_4$−MeOH[28] in refluxing Et_2O resulted in the formation of hydroxy acid **41**, the monomer used to prepare linear trimer **49**. Once again, EDCI-mediated

(21) Sha, C. K.; Tsong Shin, J.; Wang, D. C. *Tetrahedron Lett.* **1990**, *31*, 3745.

(22) The mechanism and regioselectivity of the nucleophilic attack on 2,2-dimethylaziridines depend on the degree of leaving group activation: Lin, P.-Y.; Bellos, K.; Stamm, H.; Onistschenko, A. *Tetrahedron* **1992**, *48*, 2359. Onistschenko, A.; Buchholz, B.; Stamm, H. *Tetrahedron* **1987**, *43*, 565. Stamm, H.; Assithianakis, P.; Buchholz, B.; Weib, R. *Tetrahedron Lett.* **1982**, *23*, 5021.

(23) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *59*, 1548.

(24) For extensive leading references to the reactivity of sterically hindered amines, see: Guziek, F. S.; Torres, F. F. *J. Org. Chem.* **1993**, *58*, 1604. See also: Kim, H.-O.; Gardner, B.; Kahn, M. *Tetrahedron Lett.* **1995**, *36*, 6013. Kim, H.-O.; Kahn, M. *Synlett* **1995**, 549.

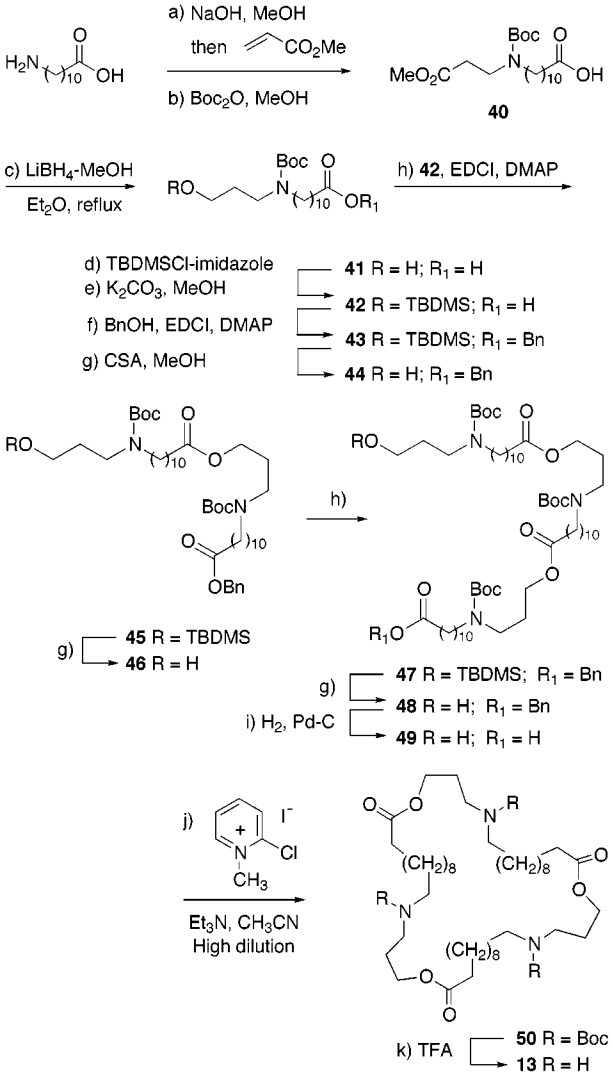
(25) The unusual stability of the intermediate ozonide in *tert*-butyl methyl ether made possible its direct treatment with 4-carboxybutyltriphenylphosphonium ylide to afford unsaturated acid **30**: Farmer, J. J. Ph.D. Thesis, Cornell University, 1999.

(26) Attempts to benzylate acid **30** in the presence of DCC resulted in a difficult isolation of the product and lower yields. See *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999; Chapter 7, p 415.

(27) Marcovici-Mizrahi, D.; Gottlieb, H. E.; Marks, V. Nudelman, A. *J. Org. Chem.* **1996**, *61*, 8402. Moraczevski, A. L.; Banaszynski, L. A.; From, A. M.; White, C. E.; Smith, B. D. *J. Org. Chem.* **1998**, *63*, 7258. Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985**, *50*, 5032.

(28) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.

Scheme 3



coupling between suitably protected monomers **42** and **44** gave dimer **45** with an overall yield of 80% from hydroxy acid **41** after TBDMS ether cleavage. Subsequent exposure of dimer **45** to a second sequence of desilylation, esterification, and protecting group removal set the stage for the crucial cyclization of linear trimer **49**. As before, macrolactonization was carried out using Mukaiyama's reagent under high dilution conditions to provide macrocyle **50**, whose amino groups were deprotected to give the targeted polyamine **13**. Including the hydrolysis step, 48-membered polyazamacrocycle **13** was obtained from precursor hydroxy acid **49** in 40% overall yield. In addition to its simplified ^{1}H NMR, 14-line ^{13}C NMR and 2D NMR spectra, the ESIMS spectrum supported the structure **13**, showing positive ions at m/z = 725, 363, and 242, corresponding to singly, doubly, and triply charged molecular ions, respectively. Although there are reports of macrolactonizations promoted by Mukaiyama's reagent that undergo undesired intermolecular dimerization,[18] no trace of hexamers could be detected by LC-ESIMS in any of the macrocyclizations reported herein. The observed selectivity indicates the enormous capability of this methodology to afford intramolecular esterifications starting from open chain hydroxy acids.

***O*-to-*N* Acyl Migration in Polyazamacrolides.** With PAML 681 and analogues in hand, we focused our study on *O*-to-*N* acyl migrations, which sequentially convert polyazamacrolides into the rearranged, ring-contracted amides. While this type of transformation is well-documented for individual structures in the literature,[7−10] polyazamacrolides **11**, **12**, and **13**, along with PAML 681, offered an excellent opportunity to study these rearrangements in a closely related group of compounds. A combination of spectroscopic and chromatographic methods allowed us to observe mono- and bisamide intermediates, to estimate relative rearrangement rates, and to investigate the effects of discrete structural modifications on polyazamacrolide reactivities.

Conversion of each polyazamacrolide into its amide counterpart was performed under identical conditions at 50 °C in sealed NMR tubes with C_6D_6 as solvent (0.015 M). Monitoring the disappearance of a ^{1}H NMR signal characteristic of the lactone moiety, as well as the appearance of diagnostic signals for the developing amide, provided a convenient way to follow the progress of the *O*-to-*N* acyl migration. In addition, complementary spectroscopic data (^{13}C NMR, 2D ^{1}H−^{13}C NMR, IR, MS) along with LC separation were fully consistent with the progressive ester to amide rearrangement. The ^{1}H NMR spectral changes with time are illustrated for polyazamacrolide **13** in Figure 6. The *O*-to-*N* acyl migration affects all the proton chemical shifts in the substrate, particularly those corresponding to methylene groups attached to heteroatoms. Protons α to the oxygen atoms (δ 4.15−4.25 ppm) move upfield (δ 3.55−3.65 ppm) as a consequence of liberating the primary hydroxyl group, while the methylene protons α to the amine experience a downfield shift (from δ 2.45−2.60 to δ 2.65−3.40 ppm) as a consequence of amide formation. Moreover, HPLC-MS analysis suggests that the individual *O*-to-*N* acyl migration steps proceed at comparable rates, resulting in the coexistence during the rearrangement process of the starting polyamine with monoamide, bisamide, and the fully rearranged trisamide.[4a,b] The progress of this rearrangement can also be followed by monitoring the disappearance of the ester carbonyl stretching band (1730 cm^{-1}) and the growth of the amide band (1625 cm^{-1}) in the IR spectra of the reaction mixture (Figure 7). Studies of the rearrangement of PAML 681, **11**, and **12** gave results entirely analogous to those observed for **13**.

Quantification of the time-dependent disappearance of methylene protons α to the ester carbonyl group in the ^{1}H NMR spectra of each of the macrocyclic lactones we studied followed first-order kinetics, affording relative rate constants for the acyl transfer in PAML 681 and the three synthetic polyazamacrolide analogues.[29] A clear but modest rate difference was observed to result from the addition of a methylene group between the O and N atoms (comparing **11** with **13**); more striking differences resulted from changing the degree of substitution adjacent to the nucleophilic amino group (comparing PAML 681 with **11** and **12**). Thus, rearrangement via the formation of a five-membered hydroxyoxazolidine intermediate was found to proceed four times faster than the rearrangement via a six-membered hydroxyoxazinane.[30] Similar differences in relative rates have been described by Bruice and Benkovic for the intramolecular attack by an amino group on a neighboring ester group in linear

(29) Observed rate constants, including contributions from all lactonic species generated during the *O*-to-*N* acyl migrations, were determined by a nonlinear least-squares analysis showing excellent fits in all cases.

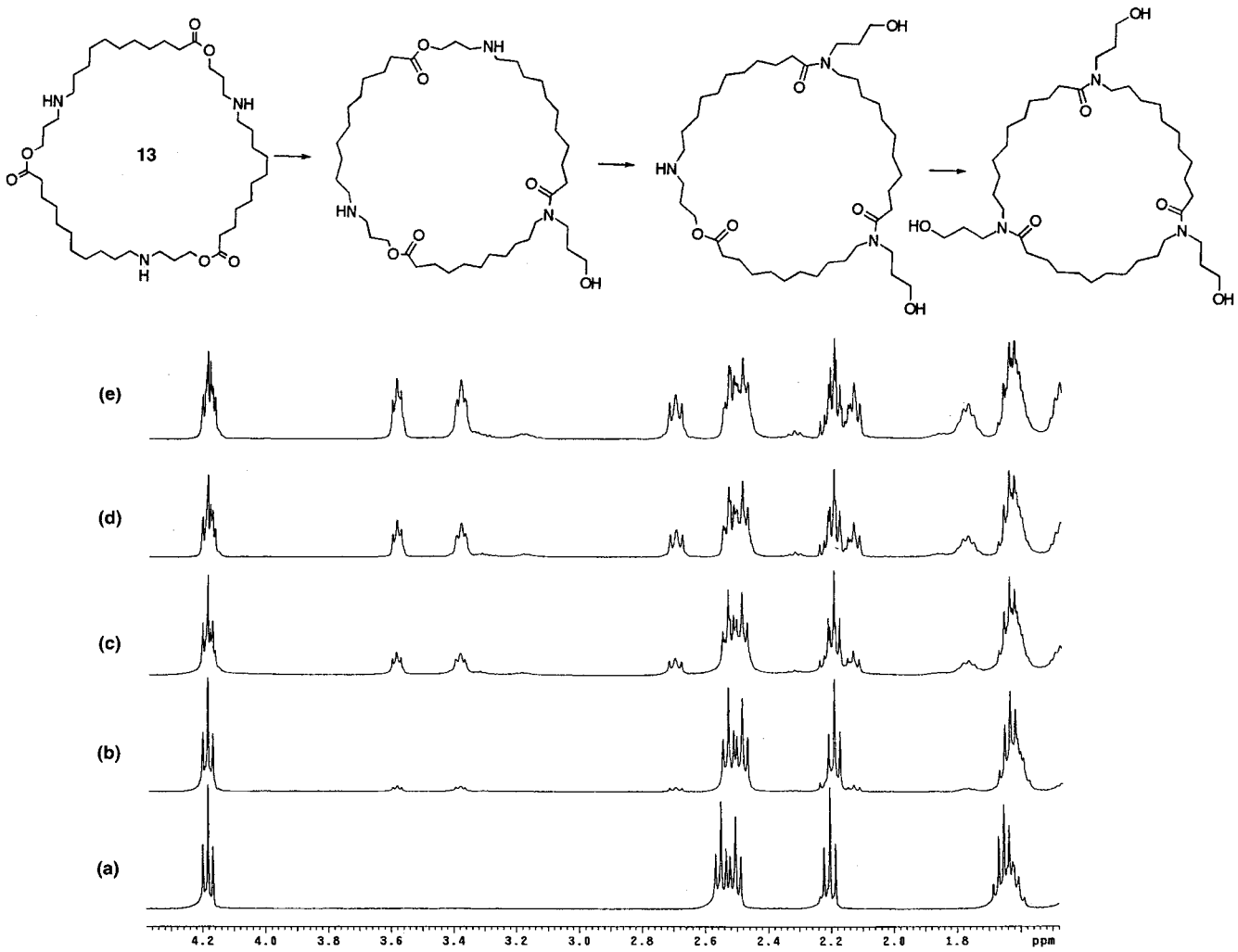


Figure 6. Monitoring of the *O*-to-*N* acyl migration of polyazamacrolide **13** by ^{1}H NMR (400 MHz, C_6D_6, 50 °C, TMS as external standard). (a) $t = 0$, (b) $t = 4$ d, (c) $t = 12$ d, (d) $t = 20$ d, (e) $t = 27$ d.

4- and 5-aminoalkanoates.[31a] These results suggest that the macrocyclic structures themselves have a negligible effect on the *O*-to-*N* acyl migrations; this conclusion is in full agreement with the obvious conformational flexibility of the original polyazamacrolides, as well as of the monoamide and bisamide intermediates formed on the way to the fully rearranged products. The larger influence of methyl group substitution adjacent to the nucleophilic nitrogen atoms of the lactone on the *O*-to-*N* acyl group migration rates proved to be somewhat of a surprise. The lowest rearrangement rate was observed for PAML 681 itself. Removal of the α-methyl group entirely (**11**) resulted in a 30-fold faster rearrangement.[24] Interestingly, addition of three additional α-methyl substituents (**12**) resulted in a 280-fold acceleration. This effect of the *gem*-dimethyl groups is particularly striking, since the substituents are not actually on the five-membered ring intermediate through which the rearrangement proceeds but lie outside the hydroxyoxazolidine ring.[30a,32] It seems conceivable that the effect of the *gem*-dimethyl group is a consequence of favoring a ground state conformation in **12**, which more closely resembles the conformation of the transition state leading to the corresponding five-membered hydroxyoxazolidine rearrangement intermediate. These observations prompted us to search for an understanding of the PAML rearrangements in terms of a conformational analysis of PAML 681, its 10-nor derivative **11** and *gem*-dimethyl analogue **12**.

Molecular mechanics calculations were performed on the PAMLs in an effort to assist the rationalization of the experimental data regarding the relative rates of rearrangement.[33] Following a considerable amount of

(30) (a) The kinetic premium on the formation of five-membered rings has been measured in terms of "effective molarity" for a variety of related lactamizations involving secondary amines: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, 183 and references therein. (b) For a discussion on the factors responsible for the efficiency of intramolecular aminolysis reactions, see: Fife, T. H.; Chauffe, L. *J. Org. Chem.* **2000**, *65*, 3579. Fife, T. H.; Duddy, N. W. *J. Am. Chem. Soc.* **1983**, *105*, 74.

(31) (a) Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1963**, *85*, 1. (b) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966; Vol. 1.

(32) The so-called "*gem*-dialkyl effect" accounts for the ease of cyclization processes upon alkyl substitution on the backbone chain: Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. Hammond, G. S. *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956. Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701. Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858. Schleyer, P. v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368. Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319. Parrill, A. L.; Dolata, D. P. *THEOCHEM, J. Mol. Struct.* **1996**, *370*, 182. Jung, M. E. *Synlett* **1999**, 843. For excellent reviews, see: Eliel, E. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 197. Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum Press: New York, 1976; Vol. I, p 43. See also: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. Keese, R.; Meyer, M. *Tetrahedron* **1993**, *49*, 2055 and references therein.

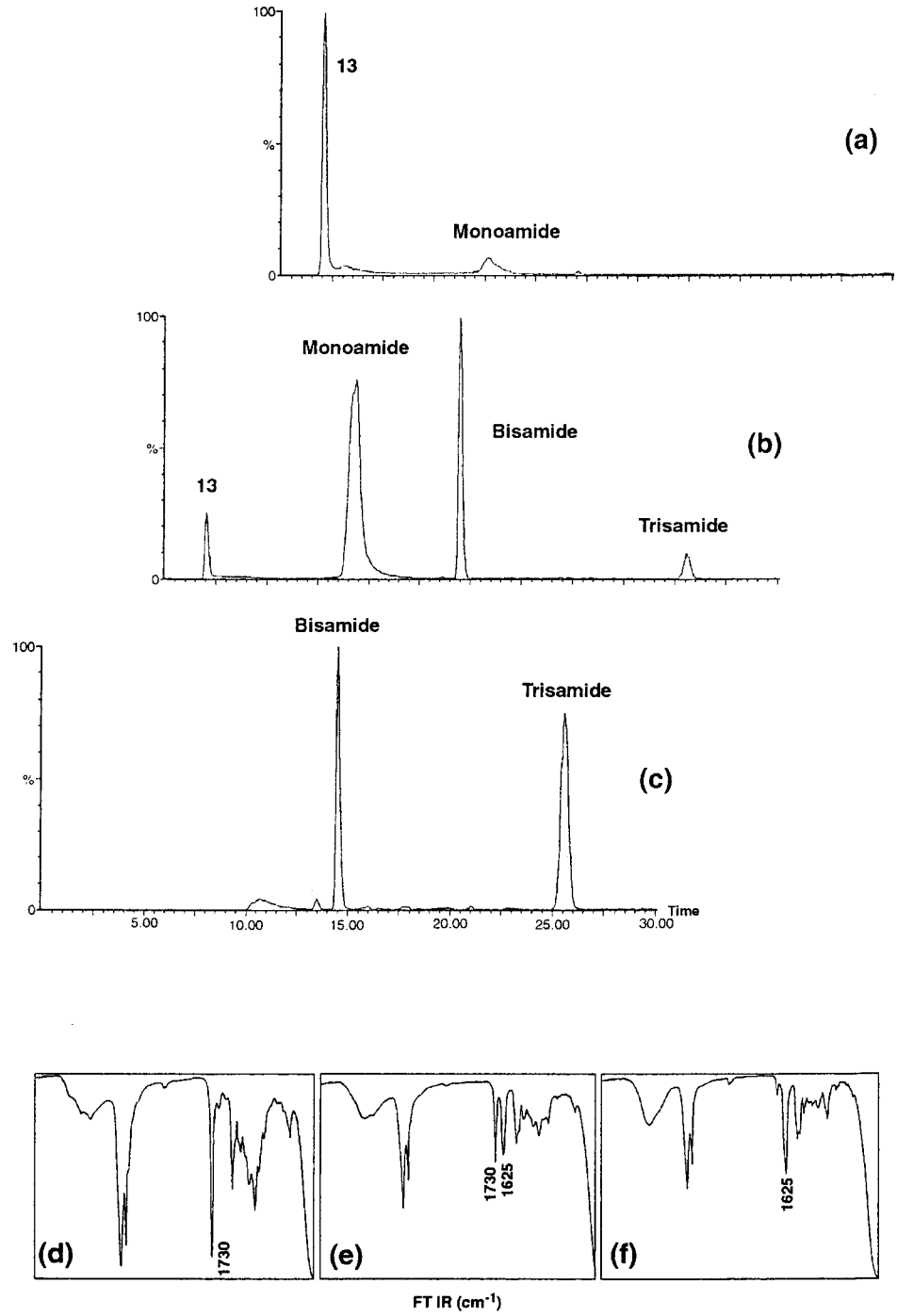


Figure 7. (1) HPLC-MS analysis of a reaction mixture for the *O*-to-*N* acyl migration of polyazamacrolide **13** (total ion current chromatogram; for each of the displayed chromatograms, the largest peak is normalized to 100%). (a) $t = 0$ d, (b) $t = 20$ d, (c) $t = 80$ d. (2) Monitoring the *O*-to-*N* acyl migration of **13** by IR spectroscopy. (d) $t = 0$ d, (e) $t = 20$ d, (f) $t = 80$ d.

computational effort, apparent global minimum conformations[34a] were found after standard Monte Carlo Multiple Minimum Search[34b] using the GLOBAL-MMX program (MMX force field) as implemented in PC Model V7.0.[35] Starting from structures with different internal coordinates, a variable number of conformational families containing conformations calculated within 3 kcal/mol of the apparent global minimum were obtained. Interestingly, despite the expected shallowness of their potential energy surface (363, (3*N*-6) degrees of freedom calculated for PAML 681), the lowest energy conformers of the polyazamacrolides were found to adopt a folded geometry in which the cavity of the macrocycle collapses. Every

(33) ^{1}H NMR spectral overlap observed for polyazamacrolides along with the formation of rearranged products precluded a conformational analysis based on vicinal coupling constants and intramolecular NOE measurements.

(34) (a) Saunders: M.; Houk, K. N.; Wu, Y.-D.; Still, C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419. Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150. (b) For the application of this MM computational protocol in the conformational analysis of simple macrocyclic structures, see: Ramírez, M. C.; Toscano, R. A.; Arnason, J.; Omar, S.; Cerda-García-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5085. Clyne, D. S.; Weiler, L. *Tetrahedron* **2000**, *56*, 1281 and references therein. Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224. Keller, T. H.; Weiler, L. *J. Am. Chem. Soc.* **1990**, *112*, 450. Kaisalo, L.; Koskimies, J.; Hase, T. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1477.

attempt to locate open annular structures proved to be unsuccessful, resulting in a significant destabilization (approximately 30 kcal/mol) above folded conformers.[36] Though the calculated structures are not fully energy minimized, the following gross structural elements were consistently found for different ground-state structures: (a) a strong conformation dependence on the presence of methyl substituents vicinal to each of the N atoms, (b) the preferred accommodation of the methyl substituents outside the ring system in the case of PAML 681, (c) the location of the *gem*-dimethyl-substituted carbon atoms in a corner position[34,36a] for analogue **12**, and (d) the more stable *s-trans* conformation of the ester function in all polyazamacrolides. These features agree with those previously found in the crystal structures of 12- and 14-membered macrolides,[36c,37] suggesting that the local environment of the functional groups plays a significant role in determining the conformational preferences of large macrocycles with a low degree of functionalization.[34,38] In addition, the conformational profiles show a remarkable tendency for favoring 1,5-intramolecular nitrogen−carbonyl interactions, which is consistent with the observed transannular acylation leading to cyclic amides.[39] The rate enhancing effect of the *gem*-dimethyl substitution in the *O*-to-*N* acylation process may be attributable to the increased population of distorted conformers that show nitrogen−carbonyl separation distances just inside the sum of the van der Waals radii for the N−C(O) atom pair.[40] This conformational preorganization of the ground-state structures contributing to the rates of intramolecular reactions has been defined by Bruice and Lightstone with the term "near attack conformation" (Figure 8).[41]

The prominence of intramolecular acyl migration in biopolymers and other natural products[5−7] has led to a large number of studies since Bergmann's pioneering investigations of amino alcohols.[42] In particular, selective amide formation by amine capture has been extensively explored in accord with its great potential for solid-phase peptide synthesis.[8] In this context, the essential features of the intramolecular *O*-to-*N* acyl migration have been

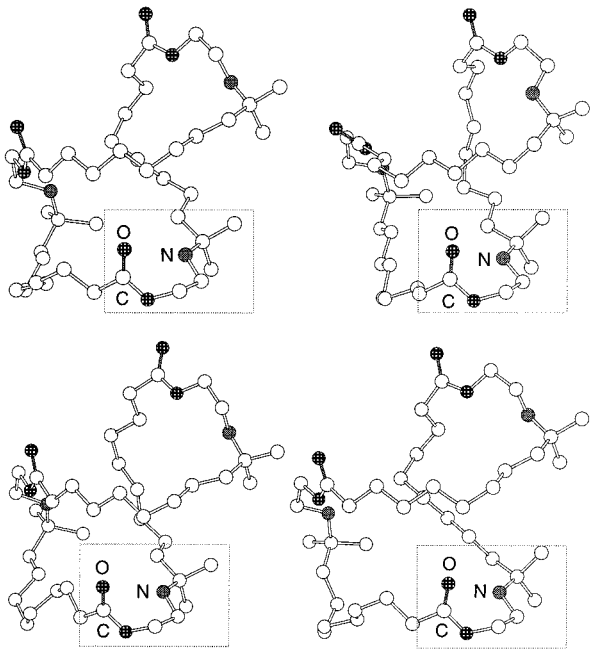


Figure 8. Calculated conformations of tris(10-methyl)PAML 681 (**12**) showing the features of near attack conformation, N−C(O) distances ~3 Å. The conformations were selected among structures obtained within 3 kcal/mol of the apparent global minimum.

detailed as follows: (a) the tetrahedral geometries at the acyl carbon and the amine nitrogen in the cyclic rate-determining transition structure,[43] (b) the trans,anti orientation of the αC−CO and N−αC bonds about the forming C−N bond,[44] and (c) the antiperiplanar arrangement of the N lone pair and the C−O alkyl bond to be broken.[45] As noted by Kemp and co-workers, the achievement of these stereoelectronic requirements is highly dependent on the conformational rigidity of the template that links the reactive amine and ester functional groups.[46] A careful examination of the oxazolidine intermediates derived from PAML 681 and its synthetic analogues by using MMX force field calculations[47] and Dreiding models suggests that the bicyclic structures can meet the stereoelectronic requirements. While the conformational flexibility of the original macrocycles allows the necessary conditions for the migration, conformational restrictions that might be imagined to result from amide bond formation in the partially rearranged lactone-lactams do not appear to significantly inhibit the mono- and bisamides from rearranging at rates comparable to those of the original macrolides since no intermediate lactone-lactam accumulation is observed.

In summary, we have carried out syntheses of several analogues of the single most important polyazamacrolide,

(35) MMX force field calculations were performed using PC Model V7.0; Serena Software, Inc. Gajewski, J. J.; Gilbert, K. E.; MacKelvey, J. *Adv. Mol. Model.* **1990**, *2*, 65.

(36) (a) The inherent skeletal strain in the open annular conformation of some cyclic polyesters has been correlated to an even number of CH_2 groups in each polymethylene chain of the corresponding hydroxy acid: Dale, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 1000. (b) For the crystal structure and distorted molecular shape of a 10-membered oxa-azamacrocycle, see: Kuksa, V.; Marshall, C.; Wardell, S.; Kong Thoo Lin, P. *Synthesis* **1999**, 1034. (c) The crystal structures of a variety of 14-membered macrolides revealed unexpected twist conformations: Keller, T. K.; Neeland, E. G.; Retting, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858. Hauske, J. R.; Gaudliana, M.; Kostek, G.; Shulte, G. *J. Org. Chem.* **1987**, *52*, 4622.

(37) Fridrichson, J.; Mathieson, A. M.; Sutor, J. *Acta Crystallogr.* **1963**, *16*, 1075.

(38) Hoffmann proposed the expression "flexible molecules with a defined shape" for molecules that show an unrestricted conformational mobility but have preferentially populated conformations: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.

(39) Existence of 1,5-intramolecular interactions (so-called "pentane interactions") has been proposed in the conformational studies of cyclododecosane and cyclohexadecane on the basis of vibrational spectrosopic analyses: Shannon, V. L.; Strauss, H. L.; Snyder, R. G.; Elliger, C. A.; Mattice, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 1947.

(40) Desper, J. M.; Gellman, S. H.; Wolf, R. E., Jr.; Cooper, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 8663. Alder, R. W.; Maunder, C. M.; Orpen, A. G. *Tetrahedron Lett.* **1990**, *31*, 6717. See also ref 38.

(41) Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127. Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595.

(42) Bergmann, M.; Brand, E.; Dreyer, F. *Ber.* **1921**, *54*, 936.

(43) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824. Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237.

(44) Kemp, D. S.; Choong, S.-L. H.; Pekaar, J. *J. Org. Chem.* **1974**, *39*, 3841.

(45) Deslongchamps, P.; Atlani, P.; Fréhel, D.; Malaval, A. *Can. J. Chem.* **1972**, *50*, 3405.

(46) Kemp, D. S.; Galakatos, N. G.; Bowen, B.; Tan, K. *J. Org. Chem.* **1986**, *51*, 1829.

(47) MM calculations (MM2 and MM3) have been used along with semiempirical MO methods to study the tetrahedral intermediates in the *N*-to-*O* acyl migration of polysubstituted 3-acetamidopropanols: Ivanov, P. M.; Pojarlieff, I. G. *An. Quim. Int. Ed.* **1996**, *92*, 171.

(48) Each ^{13}C signal corresponds to three carbons. Carbons were numbered in accordance to the numbering used for the monomeric units (see Figure 3).

PAML 681, making these nonnatural macrocyclic lactones available for chemical and/or biological studies. We have also studied the influence of small structural changes on the rates at which all of these lactones rearrange to ring-contracted lactams via intramolecular *O*-to-*N* acyl migration. The change from a methyl substituent to a *gem*-dimethyl substituent (adjacent to the nucleophilic nitrogen atom but external to the five-membered ring through which the rearrangement proceeds) results in a 280-fold rearrangement rate increase, suggesting that a detailed conformational analysis of these macrocycles should be of particular interest. The biological activities of PAML 681 and the synthesized analogues are currently being evaluated.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ or C_6D_6 on Varian XL-400 or Varian Unity 500 spectrometers operating at 499.93 or 399.86 MHz for ^1H and 100.58 MHz for ^{13}C. ^1H NMR chemical shifts are reported in δ (ppm) relative to Me_4Si as internal standard. ^{13}C NMR chemical shifts are given in δ (ppm) values relative to the solvent ($CDCl_3$ 77.00 ppm or C_6D_6 128.4 ppm). Multiplicities are indicated with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broad. Several of the NMR signals of products containing carbamate and amide moieties were doubled in the rotamer ratio as indicated by ma for major and mi for minor. IR spectra were recorded with a Perkin-Elmer 1605 series FTIR infrared spectrophotometer using NaCl pellets. Mass spectra were obtained on a Hewlett-Packard 5970 instrument. HPLC-MS analyses were carried out in a Micromass Quattro I mass spectrometer operated in positive ion electrospray mode (negative ion for carboxylic acids **37** and **49**) with a 250 mm × 4.6 mm Inertsil 5-μm ODS-3 (Metachem) HPLC column. High-resolution mass spectrometry measurements were performed in the Mass Spectrometry Laboratory at University of Illinois (Urbana-Champaign) in the FAB mode unless otherwise specified. Melting points are uncorrected. Drying of organic extracts during work up of reactions was performed over anhydrous Na_2SO_4. Chromatography refers to flash chromatography and was carried out on SiO_2 (EM Science silica gel 60, 230−400 mesh ASTM). All reactions were carried out under argon atmosphere with dry, freshly distilled solvents.

Benzyl 10-Oxodecanoate (15). To a suspension of benzyl 10-hydroxydecanoate (**14**, 2.8 g, 10 mmol), 4-methylmorpholine-4-oxide (NMO, 1.76 g, 15 mmol), and powdered 4 Å molecular sieves (550 mg/mmol) in CH_2Cl_2 (40 mL) at 0 °C was added tetrapropylammonium perruthenate (TPAP, 0.18 g, 0.5 mmol), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was filtered through a short pad of silica eluting with CH_2Cl_2, and the filtrate was concentrated to yield aldehyde **15** (4.5 g, 81%) as a pale yellow oil, which was not further purified because of its relative instability: ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 8H), 1.56−1.70 (m, 4H), 2.36 (t, J = 7.2 Hz, 2H), 2.42 (td, J = 7.2 and 2 Hz, 2H), 5.12 (s, 2H), 7.34−7.37 (m, 5H), 9.76 (t, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.6, 28.7, 28.8, 28.9, 33.9, 43.5, 66.0, 127.9, 128.2, 135.9, 173.3, 202.5.

Benzyl *N*-(*tert*-Butoxycarbonyl)-*N*-(2-hydroxyethyl)-10-aminodecanoate (16). To a solution of ethanolamine hydrochloride (995 mg, 10.4 mmol) in absolute MeOH (25 mL) were added aldehyde **15** (730 mg, 2.6 mmol) and $NaBH_3CN$ (330 mg, 5.2 mmol), and the resulting mixture was stirred at room temperature for 2 days. Next, 1 N HCl was added, and stirring was maintained for 0.5 h. MeOH was evaporated at reduced pressure, and the aqueous solution was basified with K_2CO_3 and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated in vacuo, and the intermediate amino alcohol was treated with di*tert*-butyl dicarbonate (Boc_2O, 480 mg, 2.2 mmol) in THF (60 mL) at room temperature for 3 h. The mixture was concentrated and the residue purified by chromatography (80:20 to 50:50 hexanes−Et_2O) to yield carbamate **16** as an oil (520 mg, 48%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 10H), 1.45 (s, 9H), 1.47−1.51 (m, 2H), 1.60−1.65 (m, 2H), 2.34 (t, J = 7.6 Hz, 2H), 3.16−3.27 (m, 2H), 3.36−3.40 (m, 2H), 3.70−3.74 (m, 2H), 5.11 (s, 2H), 7.35−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.5, 28.2, 28.9, 29.0, 29.1, 29.2, 34.1, 48.0 (mi) and 48.5 (ma), 49.4 (mi) and 49.9 (ma), 61.1 (mi) and 62.1 (ma), 65.9, 79.7, 128.0, 128.3, 135.9, 155.4 (mi) and 157.2 (ma), 173.5; IR 3446, 1738, 1694, 1168 cm^{-1}; MS (FAB) *m*/*z* (rel int) 422 [13, $(MH)^+$], 322 [100, $(MH\text{-}Boc)^+$], 246 (10); HRMS FAB calcd for $C_{24}H_{40}NO_5$ $[MH]^+$ 422.2906, found 422.2907.

Benzyl *N*-(*tert*-Butoxycarbonyl)-*N*-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-aminodecanoate (17). A solution of alcohol **16** (285 mg, 0.68 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl, 112 mg, 0.74 mmol), and imidazole (92 mg, 1.35 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. The reaction mixture was then diluted with CH_2Cl_2 and sequentially washed with 3% aqueous NH_4Cl, 3% aqueous Na_2CO_3, and water. The organic extracts were dried and concentrated. Chromatographic purification (60:40 hexanes−Et_2O) afforded silyl ether **17** (360 mg, quantitative) as an oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.18−1.26 (m, 10H), 1.45 (s, 9H), 1.43−1.50 (m, 2H), 1.58−1.70 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 3.20−3.30 (m, 4H), 3.66−3.72 (m, 2H), 5.11 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 18.0, 24.7, 25.7, 26.6, 28.3, 28.8, 28.9, 29.1, 29.2, 34.0, 48.0 and 48.6, 49.2 and 49.3, 61.5, 65.7, 78.7 and 78.8, 127.9, 128.3, 135.9, 155.1 and 155.3, 173.2; IR 1740, 1696, 1160 cm^{-1}; MS (ESI) *m*/*z* (rel int) 536 [100, $(MH)^+$], 480 [22, $(M\text{-}C_4H_9)^+$], 436 [22, $(MH\text{-}Boc)^+$]; HRMS FAB calcd for $C_{25}H_{46}NO_3Si$ $[MH\text{-}Boc]^+$ 436.3247, found 436.3245.

***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-aminodecanoic Acid (18).** To a solution of ester **17** (155 mg, 0.29 mmol) in EtOH (50 mL) was added 5% Pd−C (25 mg). The mixture was hydrogenated at room temperature and atmospheric pressure for 4 h. After removal of the solvent in vacuo, the residue was diluted in CH_2Cl_2, filtrated through Celite, and concentrated to yield acid **18** (128 mg, quantitative), which was used as-is in the following step: ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.20−1.40 (m, 10H), 1.45 (s, 9H), 1.43−1.50 (m, 2H), 1.62 (qn, J = 7.2 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 3.20−3.30 (m, 4H), 3.66−3.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.2, 24.6, 25.8, 26.7, 28.4, 28.9, 29.1, 29.2, 29.3, 34.0, 48.2 and 48.8, 49.3 and 49.4, 61.5 and 61.6, 79.1 and 79.2, 155.4 and 155.6, 173.3; IR 1742, 1696, 1160 cm^{-1}; MS (FAB) *m*/*z* (rel int) 346 [100, $(MH\text{-}Boc)^+$]; HRMS FAB calcd for $C_{18}H_{40}NO_3Si$ $[MH\text{-}Boc]^+$ 346.2777, found 346.2775.

Benzyl *N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*-{*N*′-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-aminodecanoyloxyethyl}-10-aminodecanoate (19). To a stirred solution of acid **18** (105 mg, 0.23 mmol), 4-(dimethylamino)pyridine (DMAP, 15 mg, 0.12 mmol), and alcohol **16** (100 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl, 50 mg, 0.26 mmol) with ice cooling. The resulting mixture was stirred at 0 °C for 2 h and then stirred at room temperature for a further 12 h. The solution was concentrated to dryness in vacuo, and the residue was taken up in AcOEt and water. The organic extract was separated and successively washed with saturated aqueous NH_4Cl, saturated aqueous Na_2CO_3, and water. The organic layer was dried and concentrated to give an oil, which was purified by chromatography (60:40 hexanes−Et_2O) to yield ester **19** (197 mg, 98%): ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.20−1.40 (m, 20H), 1.45 (s, 18H), 1.43−1.56 (m, 4H), 1.56−1.70 (m, 4H), 2.29 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 3.14−3.24 (m, 6H), 3.26−3.36 (m, 2H), 3.64−3.76 (m, 2H), 4.12−4.20 (br s, 2H), 5.12 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 24.7, 24.8, 25.8, 26.6, 26.7, 28.3, 28.4, 28.9, 29.0, 29.0, 29.1, 29.2, 29.2, 29.3, 29.3, 34.1, 34.2, 45.7 and 45.8, 47.8 and 47.9, 48.2 and 48.8, 49.3 and 49.4, 61.6, 62.1 and 62.3, 65.9, 78.9 and 79.0, 79.3 and 79.4, 128.0, 128.4, 136.0, 155.1 and 155.3, 155.4, 173.4, 173.5; IR 1740, 1698, 1160 cm^{-1}; MS (ESI) *m*/*z* (rel int)

871 [40, $(MNa)^+$], 849 [100, $(MH)^+$]; HRMS FAB calcd for $C_{42}H_{77}N_2O_7Si$ $[MH\text{-}Boc]^+$ 749.5500, found 749.5501.

Benzyl *N,N′*-Bis(*tert*-butoxycarbonyl)-*N*-[*N′*-(2-hydroxyethyl)-10-aminodecanoyloxyethyl]-10-aminodecanoate (20). To a solution of the silyl ether **19** (120 mg, 0.14 mmol) in a mixture of CH_2Cl_2−MeOH (9:1, 15 mL) at 0 °C was added camphor-10-sulfonic acid (CSA, 16 mg, 0.07 mmol), and the resulting mixture was allowed to warm at room temperature. The solvent was removed at reduced pressure, and the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated. Chromatography of the residue (20:80 hexanes−Et_2O) yielded alcohol **20** (80 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24−1.40 (m, 20H), 1.45 (s, 9H), 1.46 (s, 9H) 1.46−1.52 (m, 4H), 1.58−1.66 (m, 4H), 2.29 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 3.12−3.28 (m, 4H), 3.32−3.46 (m, 4H), 3.73 (br t, J = 4.4 Hz, 2H), 4.10−4.20 (m, 2H), 5.11 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 24.8, 26.7, 26.7, 28.3, 29.0, 29.0, 29.1, 29.2, 29.2, 29.3, 29.3, 34.2, 34.2, 45.7 and 45.8, 47.9 and 48.0, 48.7 50.1, 62.1 and 62.4, 62.6, 66.0, 79.4 and 79.5, 79.9, 128.1, 128.5, 136.0, 155.2 and 155.5, 157.6, 173.6; MS (FAB) *m*/*z* (rel int) 735 [4, $(MH)^+$], 635 [58, $(MH\text{-}Boc)^+$], 579 [100, $(M\text{-}Boc\text{-}C_4H_9)^+$], 503 (54), 246 (40); HRMS FAB calcd for $C_{36}H_{63}N_2O_7Si$ $[MH\text{-}Boc]^+$ 635.4635, found 635.4638.

Benzyl *N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-{*N′*-[*N″*-(2-{*tert*-butyldimethylsilyloxy}ethyl)-10-aminodecanoyloxyethyl]-10-aminodecanoyloxyethyl}-10-aminodecanoate (21). Trimeric ester **21** was obtained from alcohol **20** (90 mg, 0.12 mmol), acid **18** (75 mg, 0.17 mmol), DMAP (8 mg, 0.06 mmol), and EDCI·HCl (25 mg, 0.13 mmol) following the procedure for the preparation of ester **19**. Final purification was accomplished by column chromatography (50:50 hexanes−Et_2O) to afford the title compound (120 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.20−1.40 (m, 30H), 1.46 (s, 27H), 1.46−1.56 (m, 6H), 1.58−1.70 (m, 6H), 2.30 (t, J = 7.6 Hz, 4H), 2.36 (t, J = 7.6 Hz, 2H), 3.14−3.32 (m, 8H), 3.38−3.44 (m, 4H), 3.64−3.76 (m, 2H), 4.12−4.20 (m, 4H), 5.12 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, 18.2, 24.8, 24.8, 25.8, 26.7, 26.7, 28.3, 28.4, 29.0, 29.0, 29.1, 29.1, 29.2, 29.3, 29.3, 29.3, 34.1, 34.2, 45.7 and 45.8, 47.9 and 48.0, 48.2 and 48.8, 49.3 and 49.4, 61.6, 62.1 and 62.4, 65.9, 78.9 and 79.0, 79.4 and 79.5, 128.1, 128.4, 136.0, 155.1 and 155.3, 155.5, 173.5; IR 1740, 1698, 1158 cm^{-1}; MS (ESI) *m*/*z* (rel int) 1185 [80, $(MNa)^+$], 1163 [33, $(MH)^+$], 1107 [18, $(M\text{-}C_4H_9)^+$], 1063 [18, $(MH\text{-}Boc)^+$], 454 (100); HRMS FAB calcd for $C_{59}H_{108}N_3O_{11}Si$ $[MH\text{-}Boc]^+$ 1062.7753, found 1062.7756.

Benzyl *N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-{*N′*-[*N″*-(2-hydroxyethyl)-10-aminodecanoyloxyethyl]-10-aminodecanoyloxyethyl}-10-aminodecanoate (22). Operating in a manner analogous to that employed for the preparation of alcohol **20**, from **21** (110 mg, 0.09 mmol) alcohol **22** (83 mg, 84%) was obtained after chromatographic purification (Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.35 (m, 30H), 1.44−1.54 (m, 6H), 1.45 (s, 18H), 1.47 (s, 9H), 1.58−1.68 (m, 6H), 2.30 (t, J = 7.6 Hz, 4H), 2.35 (t, J = 7.6 Hz, 2H), 3.14−3.24 (m, 6H), 3.34−3.44 (m, 6H), 3.70−3.78 (m, 2H), 4.10−4.20 (m, 4H), 5.12 (s, 2H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 24.8, 26.6, 26.7, 26.7, 28.3, 29.0, 29.0, 29.0, 29.1, 29.1, 29.2, 29.2, 29.3, 29.3, 29.3, 34.1, 34.2, 45.8, 47.9, 48.6, 50.1, 62.1 and 62.4, 62.6, 65.9, 79.4 and 79.5, 79.8, 128.0, 128.4, 136.0, 155.1 and 155.5, 157.4, 173.5; IR 3466, 1740, 1696, 1160 cm^{-1}; MS (FAB) *m*/*z* (rel int) 949 [62, $(MH\text{-}Boc)^+$], 893 [100, $(M-C_4H_9)^+$], 749 (75), 579 (97), 503 (62); HRMS FAB calcd for $C_{53}H_{94}N_3O_{11}$ $[MH\text{-}Boc]^+$ 948.6888, found 948.6888.

***N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-{*N′*-[*N″*-(2-hydroxyethyl)-10-aminodecanoyloxyethyl]-10-aminodecanoyloxyethyl}-10-aminodecanoic acid (23).** Hydrogenolysis of benzyl ester **22** (83 mg, 0.08 mmol) using the conditions employed for the preparation of **18** furnished hydroxy acid **23** (73 mg, 97%): ^{1}H NMR (400 MHz, C_6D_6) δ 1.10−1.30 (m, 30H), 1.40−1.50 (m, 6H), 1.46 (s, 27H), 1.50−1.70 (m, 6H), 2.20 (br t, J = 7.6 Hz, 6H), 2.96−3.16 (m, 4H), 3.20−3.30 (m, 6H), 3.40−3.50 (m, 2H), 3.60−3.75 (m, 2H), 4.10−4.30 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 25.5, 25.6, 27.4, 27.5, 28.8, 29.7, 29.8, 29.9, 30.0, 30.0, 30.1, 30.2, 34.5, 34.7, 46.7, 48.6 (ma) and 49.1 (mi), 48.6, 50.3 (mi) and 50.8 (ma), 61.9 (mi) and 62.7 (ma), 62.8, 79.6 and 79.7, 79.8, 155.6 and 156.0, 157.7, 173.4, 177.8 and 177.9.

***N,N′,N″*-Tris(*tert*-butoxycarbonyl)-1,15,29-trioxa-4,18,-32-triazacyclodotetracontane-14,28,42-trione (24).** To a refluxing solution of 2-chloro-1-methylpyridinium iodide (37 mg, 0.15 mmol) in CH_3CN (100 mL) was added via syringe pump a mixture of the hydroxy acid **23** (35 mg, 0.04 mmol) and Et_3N (40 μL, 0.29 mmol) in CH_3CN (5 mL) over 2 h. The resulting solution was refluxed for an additional 0.5 h, cooled to room temperature, and concentrated at reduced pressure. The residue was taken up in water and extracted with Et_2O. The organic extracts were dried and concentrated, and the resulting residue was purified by flash chromatography (40:60 hexanes−Et_2O) to yield the macrocycle **24** (20 mg, 60%): ^{1}H NMR (400 MHz, C_6D_6) δ 1.10−1.30 (m, 30H, CH_2), 1.40−1.50 (m, 6H, CH_2CH_2N), 1.46 (s, 27H, CH_3), 1.50−1.65 (m, 6H, CH_2CH_2CO), 2.15−2.22 (m, 6H, CH_2CO), 3.10−3.45 (m, 12H, CH_2N), 4.15−4.30 (m, 6H, CH_2O); ^{13}C NMR (100 MHz, C_6D_6)[48] δ 25.6 (C3), 27.5 (C9), 28.8 (CH_3), 29.7, 29.8, 30.0, 30.0, (C4−C8), 34.7 (C2), 47.0 (CH_2N), 48.9 (C10), 63.0 and 63.2 (CH_2O), 79.5 (CMe_3), 155.4 and 155.8 (NCO_2), 173.2 (CO); IR 1740, 1696, 1156 cm^{-1}; MS (ESI) *m*/*z* (rel int) 984 [22, $(MK)^+$], 963 [32, $(MNa)^+$], 941 [100, $(MH)^+$], 885 [18, $(M\text{-}C_4H_9)^+$], 841 [25, $(MH\text{-}Boc)^+$], 343 (54); HRMS FAB calcd for $C_{46}H_{86}N_3O_{10}$ $[MH\text{-}Boc]^+$ 840.6313, found 840.6315.

1,15,29-Trioxa-4,18,32-triazacyclodotetracontane-14,-28,42-trione [Tris(10-nor)PAML 681, (11)]. The lactame **24** (18 mg, 19 μmol) was dissolved in trifluoroacetic acid (TFA, 190 μL) and stirrred at room temperature for 15 min. The excess of acid was removed at reduced pressure, and the residue was partitioned between 20% aqueous K_2CO_3 and Et_2O. After vigorous stirring, the aqueous phase was separated and extracted with Et_2O. The combined organic extracts were filtered through anhydrous K_2CO_3 and concentrated to give the triamine **11** (12 mg, quantitative): ^{1}H NMR (400 MHz, C_6D_6) δ 1.16−1.30 (m, 30H, CH_2), 1.34−1.44 (m, 6H, CH_2CH_2N), 1.55−1.65 (m, 6H, CH_2CH_2CO), 2.19 (t, J = 7.2 Hz, 6H, CH_2CO), 2.47 (t, J = 7.2 Hz, 6H, CH_2N), 2.64 (t, J = 5.2 Hz, 6H, NCH_2CH_2O), 4.16 (t, J = 5.2 Hz, 6H, CH_2O); ^{13}C NMR (100 MHz, C_6D_6) δ 25.7 (C3), 27.9 (C9), 29.7, 29.8, 30.1, 30.1, 30.9 (C4−C8), 34.8 (C2), 49.1 (CH_2N), 50.3 (C10), 64.5 (CH_2O), 173.4 (CO); IR 1736, 1176 cm^{-1}; MS (ESI) *m*/*z* (rel int) 641 [37, $(MH)^+$], 428 (18), 321 [100, $(M+2H)^{2+}$], 312 [55, $(M-H_2O+2H)^{2+}$], 309 (20), 227(38), 214 [100, $(M+3H)^{3+}$], 196 (65) 120 (69); HRMS FAB calcd for $C_{36}H_{70}N_3O_6$ $[MH]^+$ 640.5265, found 640.5267.

Rearrangement of Tris(10-nor)PAML 681. (A) ^{1}H NMR Spectroscopic Analysis. An NMR tube was charged with a solution of polyazamacrolide **11** (0.015 M, 0.7 mL) in C_6D_6, sealed, and placed in a thermostated bath at 50 ± 1 °C. ^{1}H NMR spectra were periodically recorded in a Varian XL-400 spectrometer (50 ± 1 °C) at intervals chosen to ensure an adequate sampling. The rearrangement was monitored by following the disappearance of the ^{1}H NMR signal characteristic of the methylene protons adjacent to the oxigen atom of the lactone moiety (δ 4.14−4.18 ppm) relative to the internal tetramethylsilane (TMS) standard. An observed rate constant (k_{obsd} = 0.084 ± 0.002) including contributions from all lactonic species generated during the *O*-to-*N* acyl migration of polyazamacrolide **11** was determined by a nonlinear least-squares analysis showing an excellent fit. Following the formation of the corresponding rearranged lactames by measuring the integration of the protons α to the hydroxyl group (δ 3.60−3.70 ppm) afforded an equivalent rate constant. Representative data are included in Supporting Information.

(B) HPLC-MS Analysis. The rearrangement was followed by analyzing aliquots of a solution of **11** (0.015 M in C_6H_6) placed in a thermostated bath at 50 ± 1 °C in a Hewlett-Packard 1090 II system equipped with a 250 mm × 4.6 mm Inertsil 5-μm ODS-3 reversed-phase column (Metachem) linked to a Micromass Quattro I mass spectrometer. The HPLC was operated with a flow rate of 1 mL/min with the folllowing

eluents: 0.05% HCO_2H/70% H_2O/30% CH_3CN for 4 min, gradient to 0.05% HCO_2H/42% H_2O/58% CH_3CN in 16 min, hold for 10 min. Operating in positive ion electrospray mode, monoamide and bisamide intermediates formed in the way to the fully rearranged product generated multiple charged ions with charge numbers corresponding to the number of basic nitrogen atoms present in the molecule. Rearranged monoamide: t_R = 2.2 min, 100%; *m/z* 640 $(MH)^+$, 321 $(M+2H)^{2+}$. Rearranged bisamide: t_R = 11.7 min, 100%; *m/z* 640 $(MH)^+$. Rearranged trisamide: t_R = 18.3 min, 100%; *m/z* 640 $(MH)^+$. These analytical data are included in the Supporting Information.

After 40 days, the totally rearranged trisamide was obtained as the only product: ^{1}H NMR (400 MHz, C_6D_6) δ 1.00−1.60 (m, 36H), 1.73 (br t, J = 7.2 Hz, 6H), 2.10−2.20 (m, 4H), 2.20−2.30 (m, 2H), 2.80−3.00 (m, 4H), 3.00−3.20 (m, 2H), 3.20−3.40 (m, 6H), 3.60−3.70 (m, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 25.9, 27.2, 29.6, 29.9, 29.9, 29.9, 29.9, 33.4, 46.5 (ma) and 46.7 (mi), 49.8 (mi) and 50.7 (ma), 61.0 (mi) and 63.2 (ma), 174.6 (mi) and 174.8 (ma); IR 3394, 1620 cm^{-1}; MS (FAB) *m/z* (rel int) 641 [100, $(MH)^+$], 623 [61, $(MH-H_2O)^+$], 578 (9), 214 (11); HRMS FAB calcd for $C_{36}H_{70}N_3O_6$ $[MH]^+$ 640.5265, found 640.5267.

***N*-(2-Methylhept-6-en-2-yl)toluene-4-sulfonamide (26).** A solution of 3-butenylmagnesium bromide in Et_2O (50 mL) was prepared from magnesium metal (0.66 g, 27.1 mmol) and 4-bromo-1-butene (2.0 mL, 20.2 mmol) and slowly added to a slurry of CuI (0.77 g, 4.0 mmol) in Et_2O (50 mL) at −78 °C. After the solution was allowed to warm to room temperature and cooled at −78 °C, a suspension of 2,2-dimethyl-1-(toluene-4-sulfonyl)aziridine (**25**, 1.3 g, 5.8 mmol) in Et_2O was added in one portion. The reaction was warmed to room temperature, stirred overnight, and quenched with a mixture of NH_4Cl−NH_4OH (4:1). The resulting mixture was stirred for 2 h, the organic layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic phases were dried and concentrated to afford a colorless oil, which was purified by chromatography (80:20 hexane−AcOEt) to yield **26** as a white solid (1.3 g, 78%), mp 62−64 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 6H), 1.30−1.38 (m, 2H), 1.45−1.50 (m, 2H), 1.94 (qt, J = 7.2 and 1.2 Hz, 2H), 2.42 (s, 3H), 4.65 (s, 1H), 4.93 (ddt, J = 10, 2 and 1.6 Hz, 1H), 4.96 (ddd, J = 17.2, 2 and 1.6 Hz, 1H), 5.72 (ddt, J = 17.2, 10.4 and 6.8 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.78 (dt, J = 8 and 2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 23.1, 27.6, 33.7, 42.2, 56.9, 114.5, 126.8, 129.3, 138.4, 140.6, 142.6; IR 1324, 1306, 1150, 1092 cm^{-1}; MS (EI) *m/z* (rel int) 281 (5, M^+), 266 [49, $(M-CH_3)^+$], 212 [100, $(M-C_5H_9)^+$], 172 [6, $(M-C_8H_{14})^+$], 155 [30, $(M-C_8H_{15}N)^+$], 91 (17); HRMS EI calcd for $C_{15}H_{23}NO_2S$ $[M]^+$ 281.1450, found 281.1456.

***N*-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-*N*-(2-methylhept-6-en-2-yl)-*p*-toluenesulfonylamide (27).** Sulfonamide **26** (1.2 g, 4.2 mmol)] was slowly added via syringe pump to a slurry of NaH (0.12 g, 5.2 mmol) in DMF (40 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h, and *tert*-(butyldimethylsilyloxy)ethyl bromide (1.1 mL, 5.1 mmol) was added dropwise. The mixture was allowed to warm to room temperature, and stirring was continued for 4 days. The reaction was quenched with water, and the resulting mixture was extracted with 90:10 pentane−Et_2O. The combined extracts were dried and concentrated to give a yellow oil. Chromatography of the residue (from 90:10 to 80:20 hexanes−Et_2O) yielded silyl ether **27** (0.95 g, 92% based on the consumption of **26**) and recovered **26** (0.54 g, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.28 (s, 6H), 1.32−1.36 (m, 2H), 1.63−1.68 (m, 2H), 1.99 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 3.45 (t, J = 7.2 Hz, 2H), 3.84 (t, J = 7.2 Hz, 2H), 4.94 (dm, J = 16.8 Hz, 1H), 4.97 (dm, J = 10.4 Hz, 1H), 5.75 (ddt, J = 16.8, 10.4 and 6.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.2, 21.4, 23.8, 25.9, 27.3, 33.9, 41.1, 47.8, 61.9, 63.6, 114.6, 126.9, 129.3, 138.3, 141.0, 142.5; IR 1156, 1090 cm^{-1}; MS (FAB) *m/z* (rel int) 440 [7, $(MH)^+$], 330 [100, $(M-C_8H_{15})^+$], 272 (41); HRMS FAB calcd for $C_{23}H_{42}NO_3SiS$ $[MH]^+$ 440.2655, found 440.2661.

***N*-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-*N*-(2-methylhept-6-en-2-yl)amine (28).** A solution of sodium naphthalenide in DME (7 mL, 0.3 M) was added dropwise to a solution of sulfonamide **27** (900 mg, 2.0 mmol) in DME (30 mL) at −78 °C until a green color persisted. The reaction mixture was warmed to room temperature and quenched with EtOH. After concentration at reduced pressure, the residue was taken up in water and extracted with Et_2O. The organic extracts were washed with saturated aqueous NaCl, dried, and concentrated to give a brown solid, which was purified by chromatography (from 95:5:0 to 78:20:2 hexanes−Et_2O−diethylamine) to yield amine **28** (340 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.05 (s, 6H), 1.35−1.40 (m, 4H), 2.02−2.06 (m, 2H), 2.61 (t, J = 5.2 Hz, 2H), 3.71 (t, J = 5.2 Hz, 2H), 4.95 (dm, J = 10 Hz, 1H), 5.01 (dm, J = 17.2 Hz, 1H), 5.81 (ddt, J = 17.2, 10 and 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 23.0, 25.8, 27.1, 34.2, 40.0, 44.0, 51.6, 62.9, 114.3, 138.7; IR 1256, 1090 cm^{-1}; MS (FAB) *m/z* (rel int) 286 [60, $(MH)^+$], 216 [100, $(M-C_5H_9)^+$] 176 [24, $(M-C_8H_{13})^+$]; HRMS FAB calcd for $C_{16}H_{36}NOSi$ $[MH]^+$ 286.2566, found 286.2566.

***N*-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-*N*-(2-methylhept-6-en-2-yl)-*tert*-butoxycarbamate (29).** A solution of amine **28** (330 mg, 1.16 mmol), Boc_2O (510 mg, 2.32 mmol), DMAP (140 mg, 1.16 mmol), and Et_3N (160 μL, 1.16 mmol) in THF (30 mL) was stirred at room temperature for 3 days. After evaporation of the solvent at reduced pressure, chromatography of the residue (from 100:0 to 96:4 hexane−AcOEt) yielded carbamate **29** (340 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.20−1.30 (m, 2H), 1.34 (s, 6H), 1.45 (s, 9H), 1.77−1.83 (m, 2H), 2.02 (br q, J = 7.2 Hz, 2H), 3.34 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 4.93 (dm, J = 10.4 Hz, 1H), 4.99 (dm, J = 17.2 Hz, 1H), 5.79 (ddt, J = 17.2, 10.4 and 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 23.9, 26.0, 28.2, 28.6, 34.1, 40.0, 47.1, 57.9, 62.6, 79.1, 114.3, 139.0, 155.3; IR 1700, 1682 cm^{-1}; MS (FAB) *m/z* (rel int) 286 [5, $(MH-Boc)^+$], 216 [100, $(M-Boc-C_5H_9)^+$], 176 [24, $(M-C_8H_{13})^+$], 162 (54); HRMS FAB calcd for $C_{16}H_{36}NOSi$ $[MH-Boc]^+$ 286.2566, found 286.2566.

(5*Z*)-*N*-(*tert*-Butoxycarbonyl)-*N*-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-amino-10-methylundec-5-enoic Acid (30). (i) To a slurry of 4-carboxytriphenylphosphonium bromide (850 mg, 1.1 mmol) in THF (10 mL) was added potassium bis(trimethylsilyl)amide (5 mL, 1 M solution in THF). After stirring for 0.5 h, the resulting slurry was decanted, and a clear ylide solution was obtained. **(ii)** Separately, a stirred solution of carbamate **27** (140 mg, 0.36 mmol) in *tert*-butyl methyl ether (10 mL) at −78 °C was charged with a constant stream of ozone. After the solution turned pale blue (∼3 min) it was purged with argon during 15 min. 4-Carboxybutyltriphenylphosphonium ylide (2.2 mL, ∼1 M solution in THF) was added via cannula dropwise, and the reaction mixture was warmed to room temperature, stirred for 2 h, and quenched with water. The crude was washed with 1:1 mixture of saturated aqueous NaCl and 1 N HCl, and the aqueous layers were extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to yield a residue that after chromatographic purification (79:20:1 hexanes−Et_2O−AcOH) afforded acid **30** (160 mg, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.20−1.30 (m, 2H), 1.35 (s, 6H), 1.47 (s, 9H), 1.70 (qn, J = 7.2 Hz, 2H), 1.77−1.83 (m, 2H), 1.99 (q, J = 7.6 Hz, 2H), 2.09 (q, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 3.35 (t, J = 6.6 Hz, 2H), 3.63 (t, J = 6.6 Hz, 2H), 5.29−5.35 (m, 1H), 5.39−5.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.3, 24.5, 26.0, 26.4, 27.4, 28.2, 28.6, 33.4, 40.1, 47.1, 57.9, 62.6, 79.2, 128.4, 131.1, 155.4, 179.2; IR 1708, 1680 cm^{-1}; MS (FAB) *m/z* (rel int) 372 [40, $(MH-Boc)^+$], 216 (100); HRMS FAB calcd for $C_{20}H_{42}NO_3Si$ $[MH-Boc]^+$ 372.2934, found 372.2934.

Benzyl (5*Z*)-*N*-(*tert*-Butoxycarbonyl)-*N*-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-amino-10-methylundec-5-enoate (31). Coupling of acid **30** (100 mg, 0.21 mmol) and benzyl alcohol (23 mg, 0.21 mmol) was performed by using the same conditions described for the preparation of ester **19**. Column chromatography (80:20 hexanes−Et_2O) yielded benzyl ester **31** (114 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$)

δ 0.06 (s, 6H), 0.90 (s, 9H), 1.17−1.25 (m, 2H), 1.34 (s, 6H), 1.45 (s, 9H), 1.70 (qn, J = 7.6 Hz, 2H), 1.75−1.82 (m, 2H), 1.97 (q, J = 7.2 Hz, 2H), 2.06 (q, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 3.34 (t, J = 6.8 Hz, 2H), 3.62 (t, J = 6.8 Hz, 2H), 5.12 (s, 2H), 5.29−5.36 (m, 1H), 5.35−5.42 (m, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 24.6, 24.9, 26.0, 26.5, 27.4, 28.2, 28.6, 33.7, 40.1, 47.1, 57.9, 62.6, 66.1, 79.0, 128.2, 128.5, 131.0, 136.1, 155.3, 173.5; IR 1740, 1698, 1680 cm^{-1}; MS (FAB) *m/z* (rel int) 462 [20, (MH-Boc)$^+$], 220 (37), 216 (100), 176 (29); HRMS FAB calcd for $C_{27}H_{48}NO_3Si$ [MH-Boc]$^+$ 462.3403, found 462.3402.

Benzyl (5*Z*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(2-hydroxyethyl)-10-amino-10-methylundec-5-enoate (32). Operating in a manner analogous to that employed for the preparation of **20**, starting from **31** (114 mg, 0.20 mmol) alcohol **32** was obtained (90 mg, quantitative) after chromatographic purification (50:50 hexanes−Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.30 (m, 2H), 1.32 (s, 6H), 1.47 (s, 9H), 1.71 (qn, J = 7.6 Hz, 2H), 1.74−1.80 (m, 2H), 1.99 (q, J = 7.2 Hz, 2H), 2.06 (q, J = 7.2 Hz, 2H), 2.36 (t, J = 6.8 Hz, 2H), 3.47 (t, J = 5.6 Hz, 2H), 3.68 (t, J = 5.6 Hz, 2H), 5.12 (s, 2H), 5.33 (td, J = 10.8 and 6.8 Hz, 1H), 5.39 (td, J = 10.8 and 6.8 Hz, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.8, 26.5, 27.3, 28.5, 33.7, 40.4, 47.4, 58.1, 64.3, 66.1, 80.3, 128.2, 128.5, 128.7, 130.7, 136.0, 157.5, 173.4.

Benzyl (5*Z*,5′*Z*)-*N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*-{*N*′-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-amino-10-methylundec-5-enoyloxyethyl}-10-amino-10-methylundec-5-enoate (33). The dimeric ester **33** was obtained from acid **30** (32 mg, 0.07 mmol), alcohol **32** (30 mg, 0.07 mmol), DMAP (4 mg, 0.03 mmol), and EDCI·HCl (13 mg, 0.07 mmol) following the procedure for the preparation of **19**. Final chromatographic purification (60:40 hexanes−Et_2O) afforded the title ester (50 mg, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.15−1.30 (m, 4H), 1.33 (s, 12H), 1.46 (s, 18H), 1.60−1.75 (m, 4H), 1.75−1.85 (m, 4H), 1.94−2.00 (m, 4H), 2.00−2.10 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 3.34 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 4.10 (t, J = 6.6 Hz, 2H), 5.12 (s, 2H), 5.30−5.40 (m, 4H), 7.27−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 24.6, 24.8, 26.0, 26.6, 26.6, 27.4, 27.5, 28.2, 28.5, 28.6, 33.7, 33.7, 40.1, 43.5, 47.2, 57.9, 58.0, 62.6, 63.4, 66.1, 79.0, 79.5, 128.2, 128.2, 128.5, 128.5, 128.6, 130.8, 131.0, 136.1, 155.1, 155.3, 173.5; IR 1740, 1700, 1682 cm^{-1}; MS (FAB) *m/z* (rel int) 801 [10, (MH-Boc)$^+$], 745 [21, (M-Boc-C_4H_9)$^+$], 515 (22), 459 (27), 216 (100), 162 (43); HRMS FAB calcd for $C_{46}H_{81}N_2O_7Si$ [MH-Boc]$^+$ 801.5813 found 801.5813.

Benzyl (5*Z*,5′*Z*)-*N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*-[*N*′-(2-hydroxyethyl)-10-amino-10-methylundec-5-enoyloxyethyl]-10-amino-10-methylundec-5-enoate (34). Proceeding from **33** (76 mg, 0.08 mmol) in the manner described for for the preparation of **20**, alcohol **34** (50 mg, 76%) was obtained after chromatographic purification (50:50 hexanes−Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.30 (m, 4H), 1.33 (s, 12H), 1.46 (s, 9H), 1.48 (s, 9H), 1.65−1.72 (m, 4H), 1.74−1.81 (m, 4H), 1.95−2.02 (m, 4H), 2.00−2.10 (m, 4H), 2.31 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 3.09 (br s, 1H), 3.46 (t, J = 6.8 Hz, 2H), 3.48 (t, J = 5.2 Hz, 2H), 3.69 (q, J = 5.2 Hz, 2H), 4.10 (t, J = 6.8 Hz, 2H), 5.12 (s, 2H), 5.28−5.42 (m, 4H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.5, 24.8, 24.8, 26.5, 26.5, 27.3, 28.2, 28.4, 28.5, 33.6, 33.7, 40.1, 40.4, 43.5, 47.4, 58.0, 58.1, 63.4, 64.1, 66.0, 79.5, 80.2, 128.1, 128.5, 128.6, 128.7, 130.7, 130.8, 136.0, 155.1, 157.4, 173.4.

Benzyl (5*Z*,5′*Z*,5″*Z*)-*N*,*N*′,*N*″-Tris(*tert*-butoxycarbonyl)-*N*-(*N*′-{*N*″-[2-(*tert*-butyldimethylsilyloxy)ethyl]-10-amino-10-methylundec-5-enoyloxyethyl}-10-amino-10-methylundec-5-enoyloxyethyl)-10-amino-10-methylundec-5-enoate (35). Following the procedure for the preparation of ester **19**, starting from acid **30** (30 mg, 0.06 mmol), alcohol **34** (50 mg, 0.06 mmol), DMAP (4 mg, 0.03 mmol), and EDCI·HCl (12 mg, 0.06 mmol), trimeric ester **35** (66 mg, 85%) was obtained as a colorless oil after chromatographic purification (60:40 hexanes−Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.18−1.26 (m, 6H), 1.33 (s, 6H), 1.34 (s, 12H), 1.45 (s, 18H), 1.46 (s, 9H), 1.63−1.72 (m, 6H), 1.77−1.82 (m, 6H), 1.90−2.00 (m, 6H), 2.00−2.10 (m, 6H), 2.30 (t, J = 7.6 Hz, 4H), 2.36 (t, J = 7.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.6 Hz, 4H), 3.62 (t, J = 6.6 Hz, 2H), 4.09 (t, J = 6.6 Hz, 4H), 5.11 (s, 2H), 5.28−5.42 (m, 6H), 7.32−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 24.5, 24.8, 26.0, 26.6, 27.4, 27.4, 27.4, 28.2, 28.5, 28.6, 33.6, 33.7, 40.1, 43.5, 47.1, 57.8, 58.0, 62.6, 63.4, 66.1, 79.0, 79.5, 128.2, 128.5, 128.5, 128.6, 130.8, 131.0, 136.0, 155.1, 155.3, 173.4; IR 1740, 1700, 1682 cm^{-1}; MS (FAB) *m/z* (rel int) 1141 [3, (MH-Boc)$^+$], 1085 [5, (M-Boc-C_4H_9)$^+$], 613 (10), 216 (100); HRMS FAB calcd for $C_{65}H_{114}N_3O_{11}Si$ [MH-Boc]$^+$ 1140.8223, found 1140.8225.

Benzyl (5*Z*,5′*Z*,5″*Z*)-*N*,*N*′,*N*″-Tris(*tert*-butoxycarbonyl)-*N*-{*N*′-[*N*″-(2-hydroxyethyl)-10-amino-10-methylundec-5-enoyloxyethyl]-10-amino-10-methylundec-5-enoyloxyethyl}-10-amino-10-methylundec-5-enoate (36). Proceeding from ester **35** (50 mg, 0.05 mmol) in the manner described for for the preparation of **19**, alcohol **36** (38 mg, 84%) was isolated after chromatographic purification (Et_2O): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16−1.30 (m, 6H), 1.33 (s, 12H), 1.34 (s, 6H), 1.45 (s, 9H), 1.46 (s, 9H), 1.48 (s, 9H), 1.64−1.72 (m, 6H), 1.75−1.83 (m, 6H), 1.99 (q, J = 6.8 Hz, 6H), 2.00−2.08 (m, 6H), 2.30 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.6 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 3.09 (br s, 1H), 3.47 (t, J = 6.4 Hz, 4H), 3.48 (t, J = 5.6 Hz, 2H), 3.69 (q, J = 5.6 Hz, 2H), 4.10 (t, J = 6.4 Hz, 4H), 5.12 (s, 2H), 5.28−5.43 (m, 6H), 7.35−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.5, 24.8, 24.8, 24.8, 26.5, 26.5, 27.3, 28.2, 28.4, 28.5, 33.6, 33.7, 40.1, 40.4, 43.5, 47.4, 58.0, 58.1, 63.4, 64.2, 66.1, 79.6, 80.2, 128.1, 128.5, 128.6, 128.7, 130.7, 130.8, 130.8, 136.0, 155.1, 157.4, 173.4.

(5*Z*,5′*Z*,5″*Z*)-*N*,*N*′,*N*″-Tris(*tert*-butoxycarbonyl)-*N*-{*N*′-[*N*″-(2-hydroxyethyl)-10-amino-10-methylundec-5-enoyloxyethyl]-10-amino-10-methylundec-5-enoyloxyethyl}-10-amino-10-methylundec-5-enoic Acid (37). Hydrogenolysis of benzyl ester **36** (38 mg, 0.03 mmol) using the conditions employed for the preparation of **18** furnished hydroxy acid **37** (30 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.20 (m, 6H), 1.24−1.30 (m, 24H), 1.33 (s, 12H), 1.34 (s, 6H), 1.46 (s, 18H), 1.48 (s, 9H), 1.58−1.63 (m, 6H), 1.72−1.80 (m, 6H), 2.30 (t, J = 7.6 Hz, 6H), 2.36 (br s, 1H), 3.47 (t, J = 6.6 Hz, 4H), 3.48 (t, J = 5.2 Hz, 2H), 3.70 (q, J = 5.2 Hz, 2H), 4.10 (t, J = 6.6 Hz, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 25.1, 25.2, 25.2, 25.6, 25.6, 28.6, 28.8, 28.9, 29.8, 29.9, 30.0, 30.0, 30.1, 30.2, 30.3, 30.7, 30.8, 34.7, 34.8, 41.1, 41.5, 44.3, 48.0, 58.5, 58.7, 64.1, 64.2, 79.7, 80.1, 155.5, 157.4, 173.4; MS (ESI) *m/z* (rel int) 1041 [45, (M-H)$^-$], 941 [5, (M-H-Boc)$^-$], 358 (44), 258 (100).

***N*,*N*′,*N*″-Tris(*tert*-butoxycarbonyl)-5,5,19,19,33,33-hexamethyl-1,15,29-trioxa-4,18,32-triazacyclododetetracontane-14,28,42-trione (38).** Following the macrolactonization procedure described for the preparation of **24**, starting from hydroxy acid **37** (30 mg, 0.03 mmol), macrocycle **38** (20 mg, 69%) was obtained after chromatography (60:40 hexanes−Et_2O): ^{1}H NMR (400 MHz, C_6D_6) δ 1.15−1.25 (m, 30H), 1.30 (s, 18H), 1.41 (s, 27H), 1.52−1.62 (m, 6H), 1.84−1.92 (m, 6H), 2.16 (t, J = 7.6 Hz, 6H), 3.46 (t, J = 6.4 Hz, 6H), 4.25 (t, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 25.2, 25.6, 28.6, 28.9, 29.8, 29.8, 30.2, 30.7, 34.8, 41.2, 44.3, 58.7, 64.1, 79.5, 155.4, 173.3; IR 1740, 1696 cm^{-1}; MS (FAB) *m/z* (rel int) 925 [14, (MH-Boc)$^+$], 869 [35, (M-Boc-C_4H_9)$^+$], 528 (54), 282 (100), 242 (60); HRMS FAB calcd for $C_{52}H_{99}N_3O_{10}$ [MH-Boc]$^+$ 925.7330, found 925.7332.

5,5,19,19,33,33-Hexamethyl-1,15,29-trioxa-4,18,32-triazacyclododetetracontane-14,28,42-trione Tris(*d*$_3$-trifluoroacetic) Salt (39). Lactame **38** (8 mg, 8 μmol) was dissolved in trifluoroacetic acid-d_4 (100 μL) and stirred at room temperature for 15 min. Evaporation of excess acid in vacuo yielded trifluoroacetic salt **39** (8 mg, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 30H), 1.54 (s, 18H), 1.50−1.70 (m, 12H), 2.35 (t, J = 7.6 Hz, 6H), 3.25−3.35 (m, 6H), 4.30−4.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 23.4, 24.5, 25.5, 28.9, 29.0, 29.1, 29.5, 33.7, 39.6, 60.2, 89.3, 114.4 (q, J = 285 Hz), 156.2 (q, J = 41 Hz), 174.3; IR 1778, 1744, 1676, 1174 cm^{-1}.

Rearrangement of Tris(10-methyl)PAML 681. The *O*-to-*N* acyl migration of polyazamacrolide **12** was monitored using ^{1}H NMR and HPLC-MS techniques in the same manner

as described for **11**. **^{1}H NMR spectroscopic analysis**: following the disappearance of the ^{1}H NMR signals characteristic of the methylene protons adjacent to the oxigen atom of the lactone moiety (δ 4.30−4.40 ppm) afforded an observed rate constant ($k_{obsd} = 0.82 \pm 0.03$). Following the formation of the corresponding rearranged lactames by measuring the integration of the protons α to the hydroxyl group (δ 3.60−3.70 ppm) afforded an equivalent rate constant. Representative data are included in Supporting Information. **HPLC-MS analysis**: rearranged monoamide: t_R = 8.9 min, 100%; *m*/*z* 725 $(MH)^+$, 363 $(M+2H)^{2+}$. Rearranged bisamide: t_R = 14.1 min, 100%; *m*/*z* 725 $(MH)^+$. Rearranged trisamide: t_R = 23.1 min, 100%; *m*/*z* 725 $(MH)^+$. These analytical data are included in the Supporting Information. After 4 d the final product was the totally rearranged trisamide: ^{1}H NMR (500 MHz, $CDCl_3$/pyridine-d_5) δ 1.24−1.36 (m, 30H), 1.52 (s, 18H), 1.50−1.54 (m, 6H), 1.60−1.64 (m, 6H), 2.18 (t, J = 7.5 Hz, 6H), 3.41 (q, J = 5 Hz, 6H), 3.71 (q, J = 5 Hz, 6H), 6.10 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/pyridine-d_5) δ 23.3, 23.4, 25.4, 25.6, 29.1, 29.1, 29.5, 36.6, 42.2, 62.2, 174.3.

***N*-(*tert*-Butoxycarbonyl)-*N*-(methoxycarbonylethyl)-11-aminoundecanoic Acid (40).** To a vigorously stirred suspension of 11-aminoundecanoic acid (10.0 g, 49.7 mmol) in MeOH (400 mL) were added NaOH pellets (2.0 g, 50 mmol). By the time the salt solubilized, a solution of methyl acrylate (2.2 mL, 25 mmol) in MeOH (20 mL) was added dropwise. After stirring at room temperature for 4 h, half of the solvent was evaporated at reduced pressure, and Boc_2O (10.9 g, 49.7 mmol) was added in one portion. The mixture was stirred at room temperature for 36 h, and the solvent was removed in vacuo. The residue was dissolved in 1 N HCl with ice cooling and immediately extracted with AcOEt. The organic extracts were dried and concentrated to give a colorless oil. Chromatographic purification (from CH_2Cl_2 to 98:2 CH_2Cl_2−MeOH) yielded acid **40** (14.9 g, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 12H), 1.46 (br s, 9H), 1.45−1.55 (m, 2H), 1.64 (q, J = 7.4 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.54−2.62 (m, 2H), 3.10−3.22 (m, 2H), 3.40−3.52 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.6, 28.3, 28.9, 29.1, 29.2, 29.4, 33.2 and 33.7, 34.0, 43.1, 47.4 and 47.8, 51.6, 79.5, 155.2 and 155.4, 172.3 and 172.5, 179.2.

***N*-(*tert*-Butoxycarbonyl)-*N*-(3-hydroxypropyl)-11-aminoundecanoic Acid (41).** To a solution of the acid **40** (5.5 g, 14.2 mmol) and MeOH (1.15 mL, 28.4 mmol) in Et_2O (250 mL) at 0 °C was added $LiBH_4$ (0.62 g, 28.4 mmol), and the resulting suspension was refluxed for 6 h. The reaction was quenched by addition of water and 1 N HCl in an ice bath, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the hydroxy acid **41** (4.75 g, 93%), which was used in the following step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 12H), 1.44 (s, 9H), 1.42−1.56 (m, 2H), 1.60−1.70 (m, 4H), 2.33 (t, J = 7.4 Hz, 2H), 3.09 (br t, J = 6.8 Hz, 2H), 3.32−3.40 (m, 2H), 3.53−3.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.7, 28.3, 28.9, 29.1, 29.2, 29.2, 29.3, 30.4, 34.0, 42.5, 47.1, 58.1, 79.9, 157.1, 178.6.

***N*-(*tert*-Butoxycarbonyl)-*N*-[3-(*tert*-butyldimethylsilyloxy)propyl]-11-aminoundecanoic Acid (42).** Hydroxy acid **41** (2.7 g, 7.6 mmol) was treated with TBDMSCl (2.5 g, 16.8 mmol) and imidazole (1.6 g, 22.9 mmol) in CH_2Cl_2 (300 mL) in the conditions described above for the preparation of **17** to give ***tert*-butyldimethylsilyl *N*-(*tert*-butoxycarbonyl)-*N*-[3-(*tert*-butyldimethylsilyloxy)propyl]-11-aminoundecanoate** as an oil (4.5 g, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.27 (s, 6H), 0.90 (s, 9H), 0.94 (s, 9H), 1.20−1.40 (m, 12H), 1.45 (s, 9H), 1.45−1.55 (m, 2H), 1.56−1.64 (m, 2H), 1.68−1.78 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 3.10−3.20 (m, 2H), 3.20−3.30 (m, 2H), 3.62 (t, J = 6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.0, 17.4, 18.1, 24.9, 25.4, 25.8, 26.7, 28.4, 29.0, 29.2, 29.2, 29.3, 29.4, 31.3 and 31.9, 35.9, 44.0, 47.2, 60.6, 78.8, 155.5, 174.2. To a solution of the above silylester (4.5 g, 7.6 mmol) in a 4:1 mixture of MeOH and water (200 mL) was added K_2CO_3 (4.5 g, 32.6 mmol), and the resulting solution was stirred at room temperature for 2 h. The MeOH was removed in vacuo, and the residue was diluted with aqueous NH_4Cl (pH 5−6) and extracted with Et_2O. The combined organic extracts were dried and concentrated to yield a residue that was dissolved in CH_2Cl_2 and filtered through Celite. Concentration of the filtrate yielded acid **42** (3.6 g, quantitative) which was used as-is in the following step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.20−1.40 (m, 12H), 1.44 (s, 9H), 1.45−1.55 (m, 2H), 1.58−1.66 (m, 2H), 1.68−1.78 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 3.10−3.20 (m, 2H), 3.20−3.30 (m, 2H), 3.62 (t, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.2, 24.7, 25.9, 26.8, 28.5, 29.0, 29.2, 29.3, 29.5, 31.4 and 32.0, 34.0, 44.2, 47.3, 60.7, 79.0, 155.6, 179.5; IR 1742, 1698, 1174 cm^{-1}. MS (FAB) *m*/*z* (rel int) 374 [100, $(MH\text{-}Boc)^+$]; HRMS FAB calcd for $C_{20}H_{44}NO_3Si$ $[MH\text{-}Boc]^+$ 374.3090, found 374.3091.

Benzyl *N*-(*tert*-Butoxycarbonyl)-*N*-[3-(*tert*-butyldimethylsilyloxy)propyl]-11-aminoundecanoate (43). Following the procedure for the preparation of **19**, acid **42** (2.0 g, 4.2 mmol) and benzyl alcohol (0.44 mL, 4.2 mmol) were coupled using DMAP (0.26 g, 2.1 mmol) and EDCI·HCl (0.82 g, 4.2 mmol). Chromatography of the resulting crude (99:1 CH_2Cl_2−MeOH) gave ester **43** (2.0 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.20−1.40 (m, 12H), 1.45 (s, 9H), 1.45−1.55 (m, 2H), 1.64 (qn, J = 7.4 Hz, 2H), 1.68−1.78 (m, 2H), 2.36 (t, J = 7.4 Hz, 2H), 3.10−3.20 (m, 2H), 3.20−3.30 (m, 2H), 3.62 (t, J = 6 Hz, 2H), 5.12 (s, 2H), 7.27−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 24.8, 25.8, 26.7, 28.3, 29.0, 29.1, 29.2, 29.4, 31.4 and 31.9, 34.1, 44.0, 47.2, 60.6, 65.8, 78.7, 128.0, 128.4, 136.0, 155.4, 173.4; MS (ESI) *m*/*z* (rel int) 586 [28, $(MNa)^+$], 564 [100, $(MH)^+$], 508 [84, $(M\text{-}C_4H_9)^+$], 464 [72, $(MH\text{-}Boc)^+$], 292 (14), 214 (16); HRMS FAB calcd for $C_{27}H_{50}NO_3Si$ $[MH\text{-}Boc]^+$ 464.3560, found 464.3558.

Benzyl *N*-(*tert*-Butoxycarbonyl)-*N*-(3-hydroxypropyl)-11-aminoundecanoate (44). Proceeding from ester **43** (0.42 g, 0.74 mmol) in the manner described for for the preparation of **20**, alcohol **44** (0.33 g, 98%) was obtained after chromatographic purification (97:3 CH_2Cl_2−MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 12H), 1.46 (s, 9H), 1.48−1.53 (m, 2H), 1.60−1.66 (m, 4H), 2.35 (t, J = 7.6 Hz, 2H), 3.06−3.16 (m, 2H), 3.32−3.40, (m, 2H), 3.50−3.60 (m, 2H), 5.12 (s, 2H), 7.27−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.7, 28.2 (ma) and 28.4 (mi), 28.9, 29.0, 29.1, 29.2, 29.3, 30.5 (ma) and 31.4 (mi), 34.1, 42.5 (ma) and 43.4 (mi), 47.0, 58.2 (ma) and 59.6 (mi), 65.9, 79.6, 128.0, 128.4, 136.0, 156.9, 173.5; IR 3448, 1738, 1694, 1670, 1168 cm^{-1}; MS (FAB) *m*/*z* (rel int) 450 [4, $(MH)^+$], 350 [100, $(MH\text{-}Boc)^+$]; HRMS FAB calcd for $C_{26}H_{44}NO_5$ $[MH]^+$ 450.3219, found 450.3219.

Benzyl-*N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*-{*N*′-[3-(*tert*-butyldimethylsilyloxy)propyl]-11-aminoundecanoyloxypropyl}-11-aminoundecanoate (45). Ester **45** was obtained starting from acid **42** (1.0 g, 2.14 mmol), alcohol **44** (0.96 g, 2.14 mmol), DMAP (0.13 g, 1.07 mmol), and EDCI·HCl (0.41 g, 2.35 mmol) following the procedure for the preparation of ester **19**. Final chromatographic purification (98:2 CH_2Cl_2−MeOH) yielded **45** (1.7 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.20−1.40 (m, 24H), 1.45 (s, 18H), 1.48−1.53 (m, 4H), 1.60−1.66 (m, 4H), 1.66−1.80 (m, 2H), 1.80−1.90 (m, 2H), 2.29 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 3.06−3.20 (m, 4H), 3.20−3.30 (m, 4H), 3.62 (t, J = 6.4 Hz, 2H), 4.08 (t, J = 6.4 Hz, 2H), 5.11 (s, 2H), 7.27−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 18.2, 24.9, 24.9, 25.9, 26.8, 28.4, 28.4, 29.1, 29.1, 29.2, 29.3, 29.4, 29.5, 29.5, 31.4, 32.0, 34.3, 44.1, 47.3, 60.7, 62.1, 66.0, 78.9, 79.2, 128.1, 128.5, 136.1, 155.6, 173.6, 173.8; IR 1738, 1694, 1174 cm^{-1}; MS (ESI) *m*/*z* (rel int) 928 [8, $(MNa)^+$], 906 [100, $(MH)^+$], 850 [8, $(M\text{-}C_4H_9)^+$], 806 [30, $(MH\text{-}Boc)^+$], 375 (33), 353 (45); HRMS FAB calcd for $C_{46}H_{85}N_2O_7Si$ $[MH\text{-}Boc]^+$ 805.6126, found 805.6130.

Benzyl *N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*-[*N*′-(3-hydroxypropyl)-11-aminoundecanoyloxypropyl}-11-aminoundecanoate (46). Proceeding from ester **45** (0.63 g, 0.70 mmol) in a manner analogous to that employed for the preparation of **20**, alcohol **46** (0.52 g, 95%) was obtained after chromatographic purification (97:3 CH_2Cl_2−MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 24H), 1.45 (s, 9H), 1.46 (s, 9H), 1.48−1.54 (m, 4H), 1.56−1.70 (m, 6H), 1.82−1.90 (m, 2H), 2.29

(t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 3.06−3.16 (m, 4H), 3.18−3.30 (m, 2H), 3.30−3.40 (m, 2H), 3.50−3.60 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 5.11 (s, 2H), 7.27−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.7, 28.2, 28.3, 28.9, 29.0, 29.0, 29.0, 29.1, 29.2, 29.3, 30.5, 34.1, 42.4, 43.9, 47.0, 47.1, 58.1 (ma) and 59.6 (mi), 61.9, 65.8, 79.0, 79.6, 127.9, 128.3, 135.9, 155.3, 156.9, 173.4, 173.6; IR 1736, 1694, 1166 cm^{-1}; MS (FAB) m/z (rel int) 791 [5, $(MH)^+$], 691 [95, (MH-Boc)$^+$], 635 [100, (M-Boc-C_4H_9)$^+$]; HRMS FAB calcd for $C_{45}H_{78}N_2O_9$ $[MH]^+$ 791.5786, found 791.5789.

Benzyl *N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-({*N′*-[*N″*-[3-(*tert*-butyldimethylsilyloxy)propyl]-11-aminoundecanoyloxypropyl}-11- aminoundecanoyloxypropyl)-11-aminoundecanoate (47). Following the procedure for the preparation of **19**, starting from **42** (0.30 g, 0.64 mmol), **46** (0.51 g, 0.64 mmol), DMAP (0.04 g, 0.32 mmol), and EDCI·HCl (0.12 g, 0.64 mmol), ester **47** (0.80 g, quantitative) was obtained after chromatographic purification (60:40 hexane−AcOEt): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.20−1.40 (m, 36H), 1.45 (s, 27H), 1.45−1.55 (m, 6H), 1.58−1.64 (m, 6H), 1.70−1.78 (m, 2H), 1.80−1.90 (m, 4H), 2.30 (t, J = 7.6 Hz, 4H), 2.35 (t, J = 7.6 Hz, 2H), 3.10−3.20 (m, 6H), 3.20−3.30 (m, 6H), 3.62 (t, J = 6.4 Hz, 2H), 4.08 (t, J = 6.4 Hz, 4H), 5.12 (s, 2H), 7.28−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 24.8, 24.8, 25.8, 26.8, 28.3, 28.4, 29.0, 29.1, 29.1, 29.2, 29.2, 29.3, 29.4, 29.5, 31.4, 32.0, 34.2, 44.0, 47.2, 60.6, 62.0, 65.9, 78.8, 79.1, 128.0, 128.4, 136.0, 155.3, 155.5, 173.5, 173.7; IR 1738, 1694, 1174 cm^{-1}; MS (ESI) m/z (rel int) 1247 [36, $(MH)^+$], 734 (46), 624 [65, $(M+2H)^{2+}$], 506 (100), 488 (47), 392 (92), 225 (78); HRMS FAB calcd for $C_{65}H_{120}N_3O_{11}Si$ [MH-Boc]$^+$ 1146.8692, found 1146.8677.

Benzyl *N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-(*N′*-{*N″*-[3-(hydroxypropyl)]-11-aminoundecanoyloxypropyl}-11-aminoundecanoyloxypropyl)-11-aminoundecanoate (48). Ester **48** (0.50 g, 96%) was obtained from **47** (0.57 g, 0.46 mmol) in a manner analogous to that employed for the preparation of alcohol **20**, after chromatographic purification (97:3 CH_2Cl_2−MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 36H), 1.44 (s, 18H), 1.45 (s, 9H), 1.45−1.55 (m, 6H), 1.58−1.64 (m, 8H), 1.80−1.90 (m, 4H), 2.28 (t, J = 7.6 Hz, 4H), 2.34 (t, J = 7.6 Hz, 2H), 3.10−3.20 (m, 6H), 3.20−3.30 (m, 4H), 3.34−3.40 (m, 2H), 3.50−3.58 (m, 2H), 4.07 (t, J = 6.4 Hz, 4H), 5.11 (s, 2H), 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 26.7, 28.3, 28.4, 29.0, 29.1, 29.1, 29.2, 29.2, 29.3, 29.4, 29.5, 30.6, 34.2, 34.2, 42.4, 44.0, 47.1, 58.1, 62.0, 65.9, 79.1, 79.6, 128.0, 128.4, 136.0, 155.4, 157.0, 173.5, 173.7.

***N,N′,N″*-Tris(*tert*-butoxycarbonyl)-*N*-(*N′*-{*N″*-[3-(hydroxypropyl)]-11-aminoundecanoyloxypropyl}-11-aminoundecanoyloxypropyl)-11-aminoundecanoic Acid (49).** Hydrogenolysis of benzyl ester **48** (113 mg, 0.10 mmol) using the conditions employed for the preparation of **18** furnished hydroxy acid **49** (85 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 36H), 1.44 (s, 18H), 1.45 (s, 9H), 1.45−1.55 (m, 6H), 1.58−1.64 (m, 8H), 1.80−1.90 (m, 4H), 2.29 (t, J = 7.6 Hz, 4H), 2.32 (t, J = 7.6 Hz, 2H), 3.04−3.20 (m, 8H), 3.20−3.30 (m, 4H), 3.34−3.40 (m, 2H), 3.50−3.58 (m, 2H), 4.07 (t, J = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.8, 28.4, 29.0, 29.1, 29.1, 29.2, 29.3, 29.3, 29.3, 29.4, 29.4, 29.5, 29.5, 30.5, 34.2, 42.5, 44.1, 47.1, 58.2, 62.0, 79.3, 79.9, 155.5, 157.2, 173.8, 177.7; MS (ESI) m/z (rel int) 1041 [100, $(M-H)^-$], 700 (37), 600 (15), 358 (68), 258 (93), 226 (47).

***N,N′,N″*-Tris(*tert*-butoxycarbonyl)-1,17,33-trioxa-5,21,-37-triazacyclooctatetracontane-16,32,48-trione (50).** Following the macrolactonization procedure described for the preparation of **24**, starting from hydroxy acid **49** (30 mg, 0.03 mmol), macrocycle **50** (12 mg, 40%) was obtained after chromatographic purification (80:20 hexane−AcOEt): ^{1}H NMR (500 MHz, C_6D_6) δ 1.20−1.40 (m, 36H, CH_2), 1.48 (s, 27H $(CH_3)_3O$), 1.45−1.55 (m, 6H, CH_2CH_2N), 1.58−1.66 (m, 6H, CH_2CH_2CO), 1.74−1.79 (m, 6H, CH_2CH_2O), 2.21 (t, J = 7.5 Hz, 6H, CH_2CO_2), 3.06−3.13 (2m, 6H, CH_2N), 3.23−3.29 (2m, 6H, $NCH_2(CH_2)_2O$), 4.08 (t, J = 6 Hz, 6H, CH_2O); ^{13}C NMR (100 MHz, C_6D_6) δ 25.7 (C3), 27.5 (C10), 28.9 (CH_3), 29.8, 29.9, 30.1, 30.2 (C4−C9), 34.8 (C2), 44.9 (NCH_2), 48.0 (C11), 62.5 (CH_2O), 79.2 (CMe_3), 155.7 (NCO), 173.2 (CO_2); IR 1738, 1694, 1174 cm^{-1}; MS (ESI) m/z (rel int) 1048 [10, $(MNa)^+$], 1042 [15, $(MNH_4)^+$], 1025 [100, $(MH)^+$], 684 (12) 513 [28, $(M+2H)^{2+}$], 485 (22); HRMS FAB calcd for $C_{52}H_{98}N_3O_{10}$ [MH-Boc]$^+$ 924.7252, found 924.7264.

1,17,33-Trioxa-5,21,37-triazacyclooctatetracontane-16,32,48-trione [tris(10-nor)PAML 681 Homologue (13)]. Deprotection of lactame **50** (12 mg, 12 μmol) as in the case of **11** yielded triamine **13** (9 mg, quantitative): ^{1}H NMR (500 MHz, C_6D_6) δ 1.24−1.35 (m, 36H, CH_2), 1.43 (qn, J = 7.5 Hz, 6H, CH_2CH_2N), 1.62 (qn, J = 7.5 Hz, 6H, CH_2CH_2CO), 1.64 (qn, J = 7.5 Hz, 6H, CH_2CH_2OCO), 2.20 (t, J = 7.5 Hz, 6H, CH_2CO_2), 2.49 (t, J = 7 Hz, 6H, CH_2N), 2.53 (t, J = 7 Hz, 6H, $NCH_2(CH_2)_2O$), 4.20 (t, J = 6.5 Hz, 6H, CH_2O); ^{13}C NMR (100 MHz, C_6D_6) δ 25.4 (C3), 27.6 (C10), 29.3, 29.5, 29.7, 29.8 (C4−C9), 30.6 (CH_2CH_2OCO), 34.8 (C2), 46.8 (NCH_2), 50.2 (C11), 62.6 (CH_2O), 173.0 (CO); IR 1736, 1176 cm^{-1}; MS (ESI) m/z (rel int) 725 [4, $(MH)^+$], 363 [63, $(M+2H)^{2+}$], 242 [100, $(M+3H)^{3+}$]; HRMS CI calcd for $C_{42}H_{82}N_3O_6$ $[MH]^+$ 724.6204, found 724.6197.

Rearrangement of Tris(10-nor)PAML 681 Homologue. The *O*-to-*N* acyl migration of polyazamacrolide **13** was monitored using ^{1}H NMR and HPLC-MS techniques in the same manner as described for **11**. **^{1}H NMR spectroscopic analysis**: following the disappearance of the ^{1}H NMR signals characteristic of the methylene protons adjacent to the oxigen atom of the lactone moiety (δ 4.25−4.35 ppm) afforded an observed rate constant (k_{obsd} = 0.020 ± 0.001). Following the formation of the corresponding rearranged lactames by measuring the integration of the protons α to the hydroxyl group (δ 3.30−3.40 ppm) afforded an equivalent rate constant. Representative data are depicted in Figure 7. Additional data are included in Supporting Information. **HPLC-MS analysis**: rearranged monoamide: t_R = 9.4 min, 100%; m/z 725 $(MH)^+$, 363 $(M+2H)^{2+}$. Rearranged bisamide: t_R = 14.6 min, 100%; m/z 725 $(MH)^+$. Rearranged trisamide: t_R = 25.6 min, 100%; m/z 725 $(MH)^+$. Representative data are depicted in Figure 7. After 180 days the final product was the rearranged trisamide: ^{1}H NMR (400 MHz, toluene-d_8) δ 1.00−1.08 (m, 6H, CH_2), 1.10−1.40 (m, 36H, CH_2), 1.42−1.50 (m, 6H, CH_2), 1.68−1.76 (m, 6H,CH_2), 2.06−2.11 (m, 6H, CH_2CO), 2.72 (br t, J = 7.6 Hz, 6H, CH_2N), 3.34 (br t, J = 5.2 Hz, 6H, NCH_2-EtOH), 3.51 (br t, J = 5.2 Hz, 6H, CH_2OH); ^{13}C NMR (100 MHz, toluene-d_8) δ 26.1 (C3), 27.4 (C10), 29.6, 29.9, 30.0, 30.1, 30.1, 31.6 (C4−C9 and CH_2CH_2OCO), 33.2 (C2), 42.1 (CH_2N), 48.0 (C11), 58.5 (CH_2OH), 173.9 (CON); IR 3400, 1621 cm^{-1}; MS (ESI) m/z (rel int) 725 [100, $(MH)^+$], 363 [70, $(M+2H)^{2+}$], 242 [17, $(M+3H)^{3+}$]; HRMS ESI calcd for $C_{42}H_{82}N_3O_6$ $[MH]^+$ 724.6203, found 724.6192.

Calculations. A molecular mechanics search for the lowest energy conformations of PAML 681, **11**, and **12** was conducted using the Global MMX (GMMX) program, a part of the PC Model V 7.0 molecular modeling program developed by Serena Software.[35] Conformational space was searched using the MMX force fields, with the Mixed search method and the H-bonds option ON. The Mixed search method alternates between the Bonds method (that selects randomly a subset of the bonds designated for rotation, causing large changes in the shape of a molecule) and the Cartesian method (in which all atoms are moved in the 3D space causing small changes in the shape of the molecule). We selected for rotation all the carbon−carbon bonds Cx−Cy and carbon−heteroatom bonds Cx−Ny and Cx−Oy, with exception of the π systems. The original structure was minimized to generate the initial minimum energy conformation; the resulting structure was then modified by the Mixed search method, and the new conformation was minimized until the gradient fell below 0.0001. After minimization, only an energy acceptable conformer that did not duplicate a previously stored one was saved, and its geometry was used to spawn a new conformer; otherwise it was rejected. Processing by GMMX was done in two stages; the first cycle randomly searched over the rotable bonds and kept all the conformers minimized within 3.5 kcal of the lowest energy conformer found during the minimization. The second cycle reminimized the structures found in the first cycle and kept only those that are within 3 kcal of the lowest

energy conformers. To ensure an exhaustive search of the potential surface, 20,000 conformations were generated and minimized from different starting structures.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **15**−**24**, **11**, **26**−**39**, **40**−**50**, and **13** and the totally rearranged products of **11**, **12**, and **13**.^{1}H NMR and HPLC-MS monitoring for the rearrangement of compounds **11**, **12**, and PAML 681. A listing of selected conformations found within 3 kcal/mol of the apparent global minimum for **11**, **12**, and PAML 681. This material is available free of charge via the Internet at http://pubs.acs.org.

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