Synthesis of Unsaturated Polyazamacrolides from the Ladybird Beetle *Subcoccinella vigintiquatuorpunctata*

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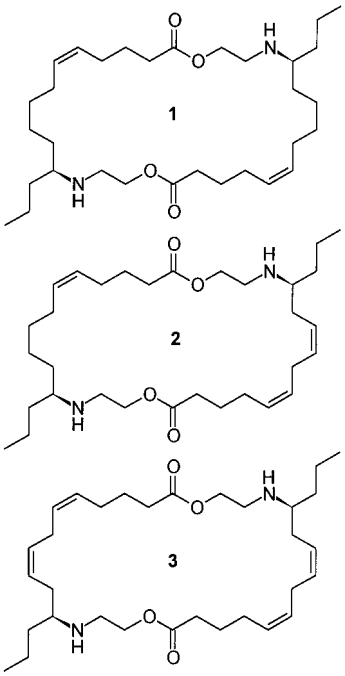
The pupal defensive secretion of the ladybird beetle *Subcoccinella vigintiquatuorpunctata* consists of a mixture of macrocyclic polyamines (polyazamacrolides, PAMLs) dominated by three dimeric, 30-membered bislactones (**1**, **2**, and **3**), which represent the three possible head-to-tail combinations of the two building blocks (*S*)-(*Z*)-11-(2-hydroxyethylamino)-5-tetradecenoic acid (**4**) and (*S*)-(5*Z*,8*Z*)-11-(2-hydroxyethylamino)-5,8-tetradecadienoic acid (**5**). We now report the synthesis of these three alkaloids via a route involving the nucleophilic opening of a chiral aziridine as a common step.

Introduction

Following our initial characterization of the novel azamacrolide alkaloids epilachnene (**6**) and epilachnadiene (**7**) as the major components of the pupal defensive secretion of the Mexican bean beetle *Epilachna varivestis*,[1] we have gone on to examine the pupal defensive chemistry of other coccinellid beetle species. In the case of the squash beetle *Epilachna borealis*, the pupal defensive secretion was shown to consist of a combinatorial library comprising hundreds of macrocyclic polyamines, the polyazamacrolides (PAMLs), along with a group of acetylated tocopherols.[2] These two sets of insect-derived alkaloids have proven to be of considerable interest as synthetic targets, and their synthesis has served to highlight some interesting methodology. Reports of the syntheses of the azamacrolides have appeared from several laboratories,[3] and in order to establish structures and stereochemistry firmly, as well as to provide sufficient material for further biological and chemical characterization, we have also completed a synthesis of epilachnene (**6**) as well as of five representative PAMLs ranging from 42- to 98-membered ring examples.[4]

Most recently, we have shown the pupal defensive secretion of the ladybird beetle *Subcoccinella vigintiquatuorpunctata* to consist of an alkaloid mixture of intermediate complexity.[5] The mixture is dominated by three dimeric, 30-membered bislactones (**1**, **2**, and **3**),



which represent the three possible head-to-tail combinations of (*S*)-(*Z*)-11-(2-hydroxyethylamino)-5-tetradecenoic acid (**4**) and (*S*)-(5*Z*,8*Z*)-11-(2-hydroxyethylamino)-5,8-tetradecadienoic acid (**5**), the acids whose monomeric lactones are epilachnene (**6**) and epilachnadiene (**7**), respectively. These three new alkaloids, characterized by a combination of HPLC-MS, NMR spectroscopy, and chemical derivatization, had not until now been fully characterized as individual compounds. We now report the synthesis and complete characterization of these unsaturated, 30-membered ring alkaloids.

Results and Discussion

Starting with the enantiomerically pure tosyl aziridine **8** previously used in our synthesis of epilachnene,[4] the two complementarily protected epilachnadienoic acid subunits (**17** and **19**) were produced via a synthetic pathway that preserves the chirality of the starting

(1) Attygalle, A. B.; McCormick, K. D.; Blankenspoor, C. L.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5204.

(2) (a) Schroeder, F. C.; Farmer, J. J.; Smedley, S. R.; Attygalle, A. B.; Eisner, T.; Meinwald, J. *J. Am. Chem. Soc.* **2000**, *122*, 3628. (b) Schroeder, F. C.; Farmer, J. J.; Attygalle, A. B.; Smedley, S. R.; Eisner, T.; Meinwald, J. *Science* **1998**, *281*, 428.

(3) (a) Furstner, A.; Langemann, K. *Synthesis* **1997**, *7*, 792. (b) King, A. G.; Meinwald, J.; Eisner, T.; Blankenspoor, C. L. *Tetrahedron Lett.* **1996**, *37*, 2141. (c) Gribble, G. W.; Silva, R. A. *Tetrahedron Lett.* **1996**, *37*, 2145. (d) Rao, B. V.; Kumar, V. S.; Nagarajan, M.; Sitaramaiah, D.; Rao, A. V. R. *Tetrahedron Lett.* **1996**, *37*, 8613. (e) Rao, B. V.; Kumar, V. S. *Tetrahedron Lett.* **1995**, *36*, 147. (f) Rao, A. V. R.; Rao, B. V.; Bhanu, M. N.; Kumar, V. S. *Tetrahedron Lett.* **1994**, *35*, 3201.

(4) (a) Farmer, J. J.; Schroeder, F. C.; Meinwald, J. *Helv. Chim. Acta* **2000**, *83*, 2594. (b) Farmer, J. J.; Attygalle, A. B.; Smedley, S. R.; Eisner, T.; Meinwald, J. *Tetrahedron Lett.* **1997**, *38*, 2787.

(5) Schroeder, F. C.; Smedley, S. R.; Gibbons, L. K.; Farmer, J. J.; Attygalle, A. B.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13387.

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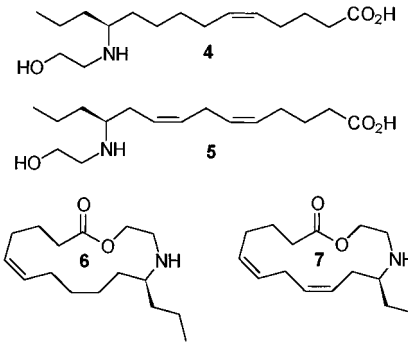


material. Using *n*-BuLi to generate the anion of THP-protected propargyl alcohol, the aziridine **8** was opened, through nucleophilic attack at the less hindered ring carbon, to give the alkyne **9** (Scheme 1). The ethanolamine moiety was next introduced by deprotonation of the sulfonamide nitrogen of **9** with sodium hydride, followed by alkylation with the TBDPS derivative of bromoethanol.[6] Deprotection and bromination of the THP-protected hydroxyl to give the propargylic bromide **11** was effected in a single step using 1,2- bis(diphenylphosphino)ethane and bromine.[7]

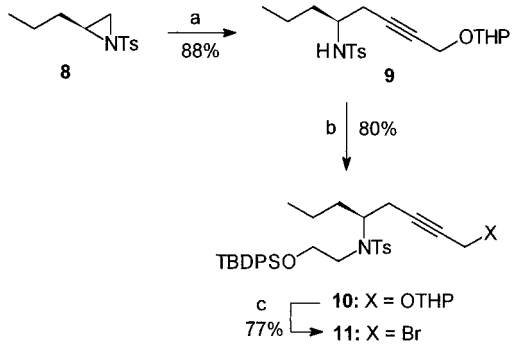
Initial attempts to couple **11** with the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester-protected[8] derivative of 5-hexynoic acid **12** using ethylmagnesium bromide and a catalytic amount of a cuprous halide were ineffective, with the reaction going only partially to completion. However, the reaction was subsequently found to proceed smoothly with *n*-BuLi and a stoichiometric amount of cuprous iodide, giving the 1,4-diyne **13** in good yield (Scheme 2).

Partial reduction of **13** with Lindlar catalyst to give the desired (*Z*,*Z*)-1,4-diene **14** proved problematic. Electrospray ionization mass spectrometric (ESI/MS) analysis of the product, along with careful inspection of its proton NMR spectrum, revealed the presence of 10−15% of a byproduct with a molecular weight greater than that of **14** by 2 amu. This byproduct, which was clearly the result of overhydrogenation, comigrated on TLC and was inseparable by normal flash chromatography. Having failed to find a more selective method of partial reduction, we decided to carry the mixture forward with the hope of being able to separate the overhydrogenated material at a later stage.

The relative stability of **14** made this a logical intermediate in the synthesis from which to remove the tosyl group, as the conditions used in its removal would be incompatible with retaining the lactone functionality once it is introduced. While our initial attempts to carry out tosylate cleavage using sodium naphthalenide tended to cause the 1,4-diene system to rearrange into conjugation, as evidenced by ^{1}H NMR spectroscopic analysis, this problem could be eliminated by carefully stopping addition of the sodium naphthalenide solution to the sulfonamide precisely at the visible endpoint of the deprotection reaction. The resulting secondary amine **15** was immediately reprotected as its BOC derivative **16**. Hydrolysis of ortho ester **16** under standard conditions (Scheme 3) gave the hydroxy-protected, BOC-derivative of (*S*)-(5*Z*,8*Z*)-11-(2-hydroxyethylamino)-5,8-tetradecadienoic acid **17**. The analogous hydroxy-protected, BOC-derivative of (*S*)-(*Z*)-11-(2-hydroxyethylamino)-5-tetradecenoic acid **20** was prepared by the synthetic pathway previously used in our synthesis of epilachnene.[4]

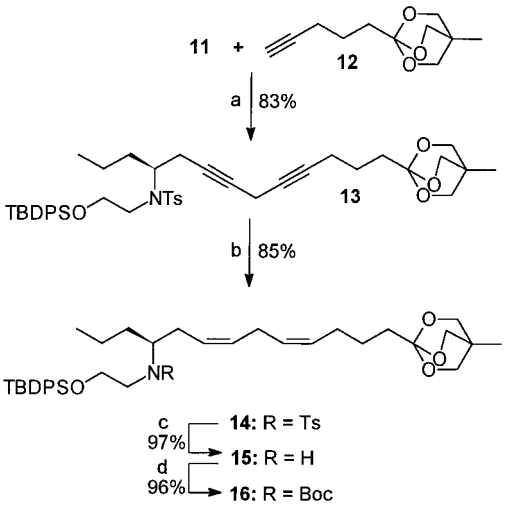
The selection of a suitable carboxylic acid protecting

Scheme 1



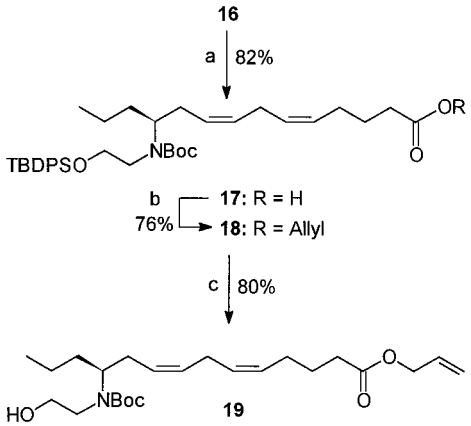
a) HC≡CCH$_2$OTHP, nBuLi, THF b) NaH, BrCH$_2$CH$_2$OTBDPS, DMF c) Ph$_2$PCH$_2$CH$_2$PPh$_2$, Br$_2$, CH$_2$Cl$_2$

Scheme 2



a) *n*-BuLi, CuI, THF b) Lindlar catalyst, H$_2$, EtOAc/EtOH c) Sodium napthalide, DME d) Boc$_2$O, THF

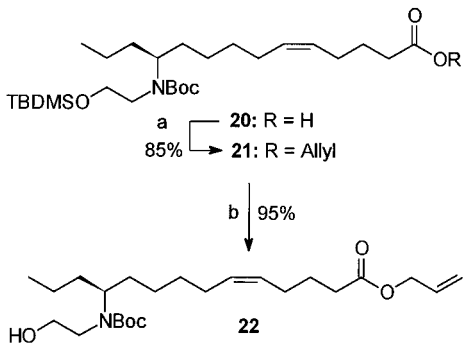
Scheme 3



a) NaHSO$_4$, DME/H$_2$O, then LiOH b) Allyl alc., DCC, DMAP, CH$_2$Cl$_2$ c) TBAF, THF

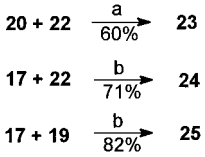
(6) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910.
(7) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.
(8) Prepared as described by: Corey, E. J.; Shimoji, K. J. *J. Am. Chem. Soc.* **1983**, *105*, 1662. For an alternate route to this ortho ester, see: Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

Scheme 4



a) Allyl alc., DCC, DMAP b) TBAF, THF

Scheme 5

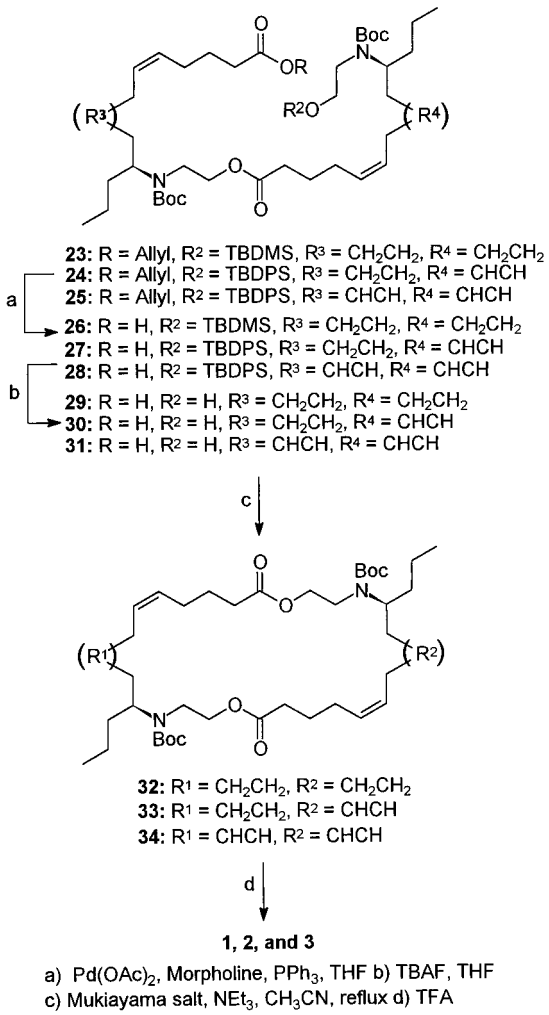


a) EDCI, DMAP, CH_2Cl_2 b) DCC, DMAP, CH_2Cl_2

group for the controlled coupling of the subunits took some consideration. We needed an ester that could later be selectively removed in the presence of the second internal ester function linking the two subunits. The fact that our target structures were unsaturated precluded the use of a benzyl ester, with subsequent removal of the benzyl group by hydrogenolysis, as had been successfully used in the synthesis of the PAMLs from *E. borealis*.[4] Protection as a methyl ester for subsequent S_N2 removal by LiI in refluxing pyridine was partially satisfactory, but the deprotection proceeded in poor yield. We eventually decided on using an allyl ester as the protecting group of choice. This functionality could be introduced under mild conditions using standard DCC coupling methodology, and the allyl group could be selectively removed with a palladium catalyst. We were concerned that the palladium catalyst might also facilitate the conversion of the skipped diene system into a conjugated system, but this was not the case. Protection of the carboxylic acid functions of **17** and **20** as their allyl esters and subsequent removal of the TBDPS and TBDMS protecting groups with TBAF gave the two carboxy- and BOC-protected derivatives of (*S*)-(5*Z*,8*Z*)-11-(2-hydroxyethylamino)-5,8-tetradecadienoic acid **19** and (*S*)-(*Z*)-11-(2-hydroxyethylamino)-5-tetradecenoic acid **22**, respectively (Schemes 3 and 4).

With the four protected subunits (**17**, **19**, **20**, and **22**) in hand, assembly of the three desired protected, open-chain dimers (**23**, **24**, and **25**) was effected by carbodiimide-promoted coupling of each of the carboxy-protected subunits with the appropriate hydroxy-protected subunit, giving the three possible linear head-to-tail combinations (Scheme 5). Removal of the allyl protecting group from each "dimer" using palladium acetate, triphenylphosphine, and morpholine in THF, followed by removal of the silyl group with TBAF, set the stage for cyclization, which was effected using Mukaiyama's methodology in yields of ca. 60% (Scheme 6).[9] At this point, the tri- and tetraenic BOC-protected alkaloids **33** and **34** were subjected to flash chromatography with 10% $AgNO_3$-impregnated silica. By this means, the small amounts of over-reduced byproducts from the earlier Lindlar hydrogenation step were readily separated, as evidenced by ESI/MS analysis.

Scheme 6



a) $Pd(OAc)_2$, Morpholine, PPh_3, THF b) TBAF, THF
c) Mukiayama salt, NEt_3, CH_3CN, reflux d) TFA

The final removal of the BOC groups from each of the cyclization products was effected with TFA, either neat in the case of **32** or added to dichloromethane solutions of **33** and **34**, giving the three natural products **1**, **2**, and **3**. The ^1H NMR spectra of the three synthetic alkaloids, obtained now for the first time, are consistent with those of the three-component, semipurified mixture that was used in the initial characterization of this pupal defensive secretion.[5]

Experimental Section

General Methods. All reagents were purchased from Aldrich or Fluka and were used without further purification. Solvents were either used as purchased or distilled using common practices where appropriate. For flash chromatography, ICN Silitech silica (32-63D, 60 Å) was used with elution solvent compositions given as volume percent per total volume. Reactions were monitored by TLC using Baker-flex (J. T. Baker) 2.5 cm × 7.5 cm plates precoated with silica gel IB-F (200 μm), and spots were visualized by UV and by anisaldehyde stain.

(9) Mukaiyama, T.; Narasaka, K.; Kikuchi, K. *Chem. Lett.* **1977**, 441. A lower yield of 46% for the triene **33** reflects the combination of the cyclization step with removal of the over-reduced byproducts by silica/silver nitrate chromatography.

4-Methyl-*N*-[(*S*)-1-propyl-5-(tetrahydropyran-2-yloxy)-pent-3-ynyl]benzenesulfonamide (9). To a stirred solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (12.87 g, 91.8 mmol) in dry THF (50 mL) under Ar was added *n*-BuLi (1.6 M in hexane; 57 mL, 91.2 mmol). After 15 min, **8** (5.46 g, 22.8 mmol) in THF (25 mL) was added dropwise, and stirring was continued at room temperature for 24 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 14% EtOAc in hexanes) to give 7.6 g (20 mmol, 88%) of **9** (diastereomeric mixture) as a pale yellow oil: $[\alpha]^{20}_D$ −77.6 (*c* 1.65, CH_2Cl_2); IR (film) 3274 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.75−7.78 (m, 2H), 7.28−7.31 (m, 2H), 4.80 (d, 1/2H, J = 9.7 Hz), 4.82 (d, 1/2H, J = 9.7 Hz), 4.77 (t, 1/2H, J = 3.4 Hz), 4.76 (t, 1/2H, J = 3.4 Hz), 4.244 (dt, 1/2H, J = 15.4, 2.2 Hz), 4.240 (dt, 1/2H, J = 15.4, 2.2 Hz), 4.175 (dt, 1/2H, J = 15.4, 2.2 Hz), 4.170 (dt, 1/2H, J = 15.4, 2.1 Hz), 3.82−3.89 (m, 1H), 3.51−3.57 (m, 1H), 3.30−3.39 (m, 1H), 2.43 (s, 3H), 2.27−2.30 (m, 2H), 1.71−1.88 (m, 2H), 1.43−1.66 (m, 6H), 1.12−1.35 (m, 2H), 0.813 (t, 1.5H, J = 7.3 Hz), 0.810 (t, 1.5H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.33, 143.32, 138.19, 138.17, 129.66, 129.65, 127.0, 97.2, 97.0, 81.4, 79.33, 79.26, 62.3, 62.1, 54.7, 54.6, 51.7, 36.42, 36.39, 30.4, 30.3, 25.4, 25.3, 25.25, 25.20, 21.5, 19.2, 19.1, 18.82, 18.81, 13.6; HRMS (FAB, *m*/*z*) calcd for $C_{20}H_{30}NO_4S$ $(M + H)^+$ 380.1896, found 380.1900.

***N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-4-methyl-*N*-[(*S*)-1-propyl-5-(tetrahydropyran-2-yloxy)pent-3-ynyl]-benzenesulfonamide (10).** To a stirred slurry of NaH (0.253 g, 10.5 mmol) in dry DMF (25 mL) under Ar at 0 °C was added **9** (2.82 g, 7.4 mmol) in DMF (10 mL) over 1 h via syringe pump. The mixture was stirred for an additional 30 min at 0 °C, and then (2-bromoethoxy)-*tert*-butyldiphenylsilane (3.83 g, 10.5 mmol) in DMF (10 mL) was added dropwise. The mixture was brought to 40 °C, and stirring was continued for 48 h. The reaction was quenched with H_2O, extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 17% EtOAc in hexanes) to give 3.94 g (5.95 mmol, 80%) of **10** (diastereomeric mixture) as a pale yellow oil: $[\alpha]^{20}_D$ +6.23 (*c* 2.66, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61−7.62 (m, 6H), 7.38−7.47 (m, 6H), 7.22−7.26 (m, 2H), 4.74−4.77 (m, 1H), 4.07−4.19 (m, 2H), 3.68−3.91 (m, 4H), 3.49−3.55 (m, 1H), 3.12−3.24 (m, 2H), 2.41 (s, 3H), 2.19 (ddt, 1H, J = 16.7, 7.6, 2.1 Hz), 2.119 (ddt, 1/2H, J = 16.7, 6.1, 2.1 Hz), 2.114 (ddt, 1/2H, J = 16.7, 6.1, 2.1 Hz), 1.02−1.88 (m, 10H), 1.06 (s, 9H), 0.76 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 137.9, 135.8, 133.65, 133.61, 130.0, 129.7, 128.0, 127.4, 96.93, 96.91, 83.0, 78.4, 63.7, 62.3, 57.5, 54.6, 45.2, 34.9, 30.5, 27.1, 25.6, 24.2, 21.7, 19.7, 19.40, 19.35, 13.85; HRMS (FAB, *m*/*z*) calcd for $C_{38}H_{52}NO_5SSi$ $(M + H)^+$ 662.3335, found 662.3333.

***N*-[(*S*)-5-Bromo-1-propylpent-3-ynyl)-*N*-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]-4-methylbenzenesulfonamide (11).** To a stirred solution of 1,2-bis(diphenylphosphino)-ethane (1.50 g, 3.77 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added bromine (1.22 g, 7.55 mmol). After 10 min, **10** (1.98 g, 2.99 mmol) in CH_2Cl_2 (7 mL) was added dropwise, and the mixture brought to room temperature. At 3.5 h, a 1:2 mixture of ether and pentane (180 mL) was added, resulting in an increased white precipitate in the already cloudy mixture. The mixture was filtered and concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, elution with 13% EtOAc in hexanes) to give 1.48 g (2.31 mmol, 77%) of **11** as a clear oil: $[\alpha]^{20}_D$ +7.58 (*c* 4.13, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63−7.68 (m, 6H), 7.39−7.47 (m, 6H), 7.24−7.27 (m, 2H), 3.72−3.89 (m, 3H), 3.74 (t, 2H, J = 2.3 Hz), 3.19 (t, 2H, J = 7.8 Hz), 2.42 (s, 3H), 2.23 (ddt, 1H, J = 2.4, 7.2, 16.8 Hz), 2.17 (ddt, 1H, J = 2.4, 6.4, 16.8 Hz), 1.43−1.52 (m, 1H), 1.06−1.28 (m, 3H), 1.07 (s, 9H), 0.78 (t, 3H, J = 7.19 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3, 137.9, 135.8, 133.59, 133.57, 130.0, 129.8, 128.0, 127.4, 84.6, 77.7, 63.6, 57.3, 45.3, 35.0, 27.1, 24.3, 21.7, 19.8, 19.3, 15.3, 13.9; HRMS (FAB, *m*/*z*) calcd for $C_{33}H_{43}BrNO_3SSi$ $(M + H)^+$ 640.1916, found 640.1918.

***N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-4-methyl-*N*-[(*S*)-10-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-propyldeca-3,6-diynyl]benzenesulfonamide (13).** To a stirred slurry of **12** (0.331 g, 1.69 mmol) and CuI (0.316 g, 1.66 mmol) in dry THF (2 mL) under Ar at −170 °C was added *n*-BuLi (1.60 M in hexane, 1.20 mL, 1.92 mmol). After 15 min, **11** (0.857 g, 1.34 mmol) in THF (4.5 mL) was added, the mixture was slowly brought to 35 °C, and stirring was continued for 27 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extract was dried (K_2CO_3), filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 33% ether in hexanes containing 2% Et_3N) to give 0.837 g (1.11 mmol, 83%) of **13** as a pale yellow oil: $[\alpha]^{25}_D$ +5.3 (*c* 0.89, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63−7.67 (m, 6H), 7.37−7.48 (m, 6H), 7.23−7.26 (m, 2H), 3.89 (s, 6H), 3.87 (dt, 1H, J = 9.1, 5.9 Hz), 3.74−3.8 (m, 1H), 3.70 (dt, 1H, J = 9.1, 5.9 Hz), 3.21 (ddd, 1H, J = 14.8, 9.0, 5.9 Hz), 3.15 (ddd, 1H, J = 14.8, 9.0, 5.9 Hz), 2.92 (quin, 2H, J = 2.4 Hz), 2.41 (s, 3H), 2.18 (tt, 2H, J = 7.1, 2.4 Hz), 2.09 (ddt, 1H, J = 16.7, 7.6, 2.4 Hz), 2.02 (ddt, 1H, J = 16.7, 6.3, 2.4 Hz), 1.46−1.79 (m, 5H), 1.10−1.25 (m, 3H), 1.06 (s, 9H), 0.80 (s, 3H), 0.77 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2, 137.9, 135.7,133.65, 133.61, 129.97, 129.95, 129.7, 128.0, 127.4, 109.1, 80.3, 77.4, 77.1, 74.4, 72.8, 63.7, 57.6, 45.1, 35.9, 35.2, 30.4, 27.1, 23.8, 22.8, 21.7, 19.7, 19.3, 18.7, 14.8, 13.9, 9.9; HRMS (FAB, *m*/*z*) calcd for $C_{44}H_{58}NO_6SSi$ $(M + H)^+$ 756.3754, found 756.3740.

***N*-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-4-methyl-*N*-[(*S*)-(3*Z*,6*Z*)-10-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-propyldeca-3,6-dienyl]benzenesulfonamide (14).** To a solution of **13** (8.5 mg, 11 μmol) in 2:1 EtOAc/EtOH (300 μL) was added Lindlar catalyst (1 mg). The reaction was stirred under a positive pressure of hydrogen and followed by TLC. After 1.5 h, the mixture was filtered and concentrated in vacuo to give 8.5 mg (11 μmol) of **14** as a mixture containing approximately 15% of a second compound that gives $(M + H)^+$ of 2 amu greater than that of **14** by ESI/MS: $[\alpha]^{25}_D$ −6.27 (*c* 6.05, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60−7.69 (m, 6H), 7.37−7.47 (m, 6H), 7.22−7.25 (m, 2H), 5.37 (dtt, 1H, J = 10.7, 7.3, 1.6 Hz), 5.18−5.26 (m, 2H), 5.04−5.11 (m, 1H), 3.903 (dt, 1H, J = 9.9, 5.6 Hz), 3.895 (s, 6H), 3.73 (dt, 1H, J = 9.9, 5.5 Hz), 3.55−3.63 (m, 1H), 3.21 (ddd, 1H, J = 14.8, 10.0, 5.7 Hz), 3.06 (ddd, 1H, J = 14.8, 10.0, 5.6 Hz), 2.49−2.66 (m, 2H), 2.40 (s, 3H), 1.96−2.05 (m, 3H), 1.64−1.76 (m, 3H), 1.48−1.56 (m, 2H), 1.07 (s, 9H), 0.84−1.29 (m, 4H), 0.80 (s, 3H), 0.73 (t, 3H, J = 7.2 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 138.1, 135.8, 133.75, 133.70, 130.3, 130.2, 129.95, 129.94, 129.7, 127.9, 127.8, 127.4, 126.0, 109.2, 72.8, 63.8, 58.6, 44.8, 36.4, 35.3, 31.3, 30.4, 27.14, 27.10, 25.9, 23.3, 21.7, 19.9, 19.4, 14.7, 13.9; HRMS (FAB, *m*/*z*) calcd for $C_{44}H_{62}NO_6SSi$ $(M + H)^+$ 760.4067, found 760.4065.

[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-[(*S*)-(3*Z*,6*Z*)-10-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-propyldeca-3,6-dienyl]amine (15). A mixture of sodium metal (65 mg, 2.8 mmol) and naphthalene (200 mg, 1.6 mmol) in dry DME was stirred under Ar at room temperature for 3 h to give a solution of sodium naphthalenide. This solution was added dropwise to a stirred solution of **14** (58 mg, 76 mmol) in dry DME at −75 °C until a dark green color persisted. The mixture was slowly brought to room temperature, quenched with EtOH, and concentrated in vacuo to give a solid white residue, which was taken up in H_2O and extracted with Et_2O. The organic extract was dried (K_2CO_3), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 33% EtOAc in hexanes containing 2% Et_3N) to give 45 mg (110 μmol, 97%) of **15** as a pale yellow oil: $[\alpha]^{20}_D$ −4.97 (*c* 4.68, CH_2Cl_2); IR (film) 3324 (w, br) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66−7.69 (m, 4H), 7.36−7.45 (m, 6H), 5.30−5.49 (m, 4H), 3.89 (s, 6H), 3.78 (t, 2H, J = 5.4 Hz), 2.69−2.86 (m, 4H), 2.52−2.60 (m, 1H), 2.19 (t, 2H, J = 6.3 Hz), 2.06 (q, 2H, J = 7.3 Hz), 1.64−1.72 (m, 2H), 1.30−1.56 (m, 6H), 1.05 (s, 9H), 0.92 (t, 3H, J = 6.9), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 133.90, 133.87, 130.5, 130.0, 129.8, 128.3, 127.8, 127.0, 109.2, 72.8, 63.6, 57.7, 49.4, 36.6,

36.4, 32.2, 30.4, 27.2, 27.0, 26.1, 23.4, 19.4, 19.3, 14.8, 14.6; HRMS (FAB, *m*/*z*) calcd for $C_{37}H_{56}NO_4Si$ $(M + H)^+$ 606.3979, found 606.3978.

[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-[(*S*)-(3*Z*,6*Z*)-10-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-1-propyldeca-3,6-dienyl]carbamic Acid Dimethylethyl Ester (16). To a stirred solution of **15** in THF (0.5 mL) was added di-*tert*-butyl dicarbonate (25 mg, 0.11 mmol). The mixture was stirred at room temperature for 17 h and then concentrated under a stream of Ar. The residue was purified by flash chromatography (silica gel, elution with 9% EtOAc in hexanes containing 2% Et_3N) to give 43 mg (61 μmol, 96%) of **16** as a clear oil: $[\alpha]^{20}_D$ −9.75 (*c* 4.22, CH_2Cl_2); IR (film) 1688 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.66−7.69 (m, 4H), 7.37−7.45 (m, 6H), 5.20−5.40 (m, 4H), 3.90 (s, 6H), 3.61−3.94 and 3.09−3.29 (2m, 5H total), 2.61−2.77 (m, 2H), 2.13 (t, 2H, J = 7.0 Hz), 1.92−2.15 (m, 2H), 1.65−1.73 (m, 2H), 1.48−1.57 (m, 2H), 1.36 and 1.43 (2s, 9H total), 1.15−1.39 (m, 4H), 1.05 and 1.06 (2s, 9H), 0.81−0.84 (m, 3H), 0.80 (s, 3H); ^{13}C NMR (this compound did not give a suitable ^{13}C NMR spectrum);[10] HRMS (FAB, *m*/*z*) calcd for $C_{35}H_{52}NO_3Si$ [(M-Boc) + H]$^+$ 562.3716, found 562.3716.

(*S*)-(5*Z*,8*Z*)-11-[[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-(dimethylethoxycarbonyl)amino]tetradeca-5,8-dienoic Acid (17). A stirred solution of **16** (105 mg, 148 μmol) in 5:1 DME/H_2O (7 mL) at 0 °C was brought to pH 3 by the addition of aqueous sodium bisulfate (3 drops of a 0.173 g/L solution). At 1 h, the mixture was brought to pH 12 with aqueous lithium hydroxide (11 drops of a 10.25 g/L solution) and then brought to room temperature. This pH was maintained, and stirring was continued for 8 h. The mixture was brought to pH 4 with aqueous sodium bisulfate and extracted with ether. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 17% EtOAc in hexanes containing 1% HOAc) to give 75.7 mg (122 μmol, 82%) of **17** as a clear oil: $[\alpha]^{20}_D$ −11.2 (*c* 1.79, CH_2Cl_2); IR (film) 3100 (br), 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.66−7.69 (m, 4H), 7.36−7.45 (m, 6H), 5.23−5.45 (m, 4H), 3.64−3.91 (m, 3H), 3.13−3.31 (m, 2H), 2.65−2.82 (m, 2H), 2.34 (t, 2H, J = 6.8), 2.09−2.16 (m, 4H), 1.61−1.75 (m, 2H), 1.43 and 1.36 (2s, 9H total), 1.14−1.39 (m, 4H), 1.05 and 1.06 (2s, 9H total), 0.80−0.84 (m, 3H); HRMS (FAB, *m*/*z*) calcd for $C_{32}H_{48}NO_3Si$ [(M-Boc) + H]$^+$ 522.3403, found 522.3401.

(*S*)-(5*Z*,8*Z*)-11-[[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-(dimethylethoxycarbonyl)amino]tetradeca-5,8-dienoic Acid Allyl Ester (18). To a stirred solution of **17** (33 mg, 53 μmol), allyl alcohol (7 mg, 120 μmol), and DMAP (7 mg, 57 μmol) in CH_2Cl_2 (0.75 mL) was added DCC (1 M in CH_2Cl_2; 60 μL, 60 μmol). The mixture was stirred under Ar at room temperature for 18 h and then concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, elution with 5% EtOAc in hexanes) to give 27 mg (40 μmol, 76%) of **18** as a pale yellow oil: $[\alpha]^{20}_D$ −10.8 (*c* 1.69, CH_2Cl_2); IR (film) 1738, 1692 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.66−7.69 (m, 4H), 7.36−7.46 (m, 6H), 5.93 (ddt, 1H, J = 17.1, 10.3, 5.7 Hz), 5.26−5.40 (m, 4H), 5.24 (dq, 1H, 10.4, 1.4 Hz), 5.32 (dq, 1H, 17.1, 1.5 Hz), 4.58 (dt, 2H, J = 5.8, 1.5 Hz), 3.62−3.80 and 3.90−3.97 (2m, 3H total), 3.09−3.31 (m, 2H), 2.63−2.78 (m, 2H), 2.35 (t, 2H, J = 7.6 Hz), 1.92−2.17 (m, 4H), 1.72 (quin, 2H, J = 7.4 Hz), 1.36 and 1.44 (2s, 9H total), 1.15−1.38 (m, 4H), 1.05 and 1.06 (2m, 9H total), 0.83 and 0.82 (2t, 3H total, J = 7.4 Hz for both); HRMS (FAB, *m*/*z*) calcd for $C_{35}H_{52}NO_3Si$ [(M-Boc) + H]$^+$ 562.3716, found 562.3716.

(*S*)-(5*Z*,8*Z*)-11-[*tert*-Butoxycarbonyl-(2-hydroxyethyl)-amino]tetradeca-5,8-dienoic Acid Allyl Ester (19). To a stirred solution of **18** (9.6 mg, 15 μmol) in THF (0.4 mL) was added TBAF (1 M in THF; 19 μL, 19 μmol). At 2 h, the mixture was concentrated under a stream of N_2, and the residue was purified by flash chromatography (silica gel, elution with 29% EtOAc in hexanes) to give 5.1 mg (12 μmol, 80%) of **19** as a clear oil: $[\alpha]^{20}_D$ −17.4 (*c* 0.90, CH_2Cl_2); IR (film) 3448 (br), 1738, 1690 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.93 (ddt, 1H, J = 17.1, 10.4, 5.8 Hz), 5.34−5.44 (m, 4H), 5.32 (dq, 1H, J = 17.1, 1.4 Hz), 5.24 (dq, 1H, J = 10.4, 1.4 Hz), 4.59 (dt, 2H, J = 5.8, 1.4 Hz), 3.63−4.11 and 3.17−3.35 (2m, 5H total), 2.72−2.82 (m, 2H), 2.36 (t, 2H, 7.5 Hz), 2.09−2.33 (m, 4H), 1.72 (quin, 2H, J = 7.5 Hz), 1.47 (s, 9H), 1.25−1.51 (m, 4H), 0.92 (t, 3H, 7.2 Hz); HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{42}N_1O_5$ $(M + H)^+$ 424.3063, found 424.3084.

(*S*)-(5*Z*,8*Z*)-11-[*tert*-Butoxycarbonyl-(2-{(*S*)-(5*Z*-8*Z*)-11-[[2-(*tert*-butyldiphenylsilanyloxy)ethyl](dimethylethoxycarbonyl)amino]tetradeca-5,8-dienlyloxy}ethyl)-amino]tetradeca-5,8-dienoic Acid Allyl Ester (25). To a stirred solution of **19** (11.9 mg, 28.1 μmol), DMAP (3.6 mg, 29 μmol), and DCC (1 M in CH_2Cl_2,, 30 μl, 30 μmol) in CH_2Cl_2 (0.25 mL) was added **17** (17.7 mg, 28.5 μmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 4.5 h and then concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, elution with 11% EtOAc in hexanes) to give 23.6 mg (23.0 μmol, 82%) of **25** as a pale yellow oil: $[\alpha]^{20}_D$ −14.4 (*c* 1.61, CH_2Cl_2); IR (film) 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.65−7.69 (m, 4H), 7.36−7.45 (m, 6H), 5.92 (ddt, 1H, J = 17.2, 10.4, 5.7 Hz), 5.22−5.40 (m, 8H), 5.32 (dq, 1H, J = 17.1, 1.5 Hz), 5.24 (dq, 1H, J = 10.4, 1.4 Hz), 4.58 (dt, 2H, J = 5.8, 1.4 Hz), 4.13 and 4.17 (2t, 2H total, J = 6.6 Hz for both), 3.61−4.06 (m, 4H), 3.09−3.36 (m, 4H), 2.63−2.83 (m, 4H), 2.36 (t, 2H, J = 7.7 Hz), 1.93−2.36 (m, 10H), 1.72 (quin, 2H, J = 7.3 Hz), 1.66−1.74 (m, 2H), 1.458 and 1.462 (2s, 9H total), 1.36 and 1.43 (2s, 9H total), 1.14−1.39 (m, 8H), 1.046 and 1.053 (2s, 9H total), 0.91 (t, 3H, J = 7.0 Hz), 0.80−0.84 (m, 3H); HRMS (ESI, *m*/*z*) calcd for $C_{61}H_{95}N_2O_9Si$ $(M + H)^+$ 1027.6807, found 1027.6723.

(*S*)-(5*Z*,8*Z*)-11-[*tert*-Butoxycarbonyl-(2-{(*S*)-(5*Z*-8*Z*)-11-[[2-(*tert*-butyldiphenylsilanyloxy)ethyl](dimethylethoxycarbonyl)amino]tetradeca-5,8-dienlyloxy}ethyl)-amino]tetradeca-5,8-dienoic Acid (28). To solution of **25** (20.4 mg, 19.9 μmol) in THF (0.5 mL, purged with Ar) was added palladium(II) acetate (approximately 0.3 mg, 1 μmol), morpholine (2.2 mg, 25 μmol), and triphenylphosphine (8.2 mg, 31 μmol). The mixture was stirred under Ar for 7 h. Aqueous hydrochloric acid (1.0 N) was added, and the mixture was extracted with ether. The organic extract was concentrated under a stream of N_2, and the residue was purified by flash chromatography (silica gel, 9% EtOAc in hexanes containing 1% HOAc) to give 17.8 mg (18.0 μmol, 90%) of **28** as a pale yellow oil: $[\alpha]^{20}_D$ −13.1 (*c* 1.49, CH_2Cl_2); IR (film) 3200 (br), 1738, 1692 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.66−7.69 (m, 4H), 7.37−7.45 (m, 6H), 5.27−5.46 (m, 8H), 3.62−4.21 (m, 6H), 3.11−3.34 (m, 4H), 2.64−2.86 (m, 4H), 1.92−2.38 (m, 12H), 1.68−1.74 (m, 4H), 1.15−1.51 (m, 26H), 1.05 (s, 9H), 0.91 (t, 3H, J = 7.3 Hz), 0.80−0.84 (m, 3H) HRMS (ESI, *m*/*z*) calcd for $C_{58}H_{91}N_2O_9Si$ $(M + H)^+$ 987.6470, found 987.6494.

(*S*)-(5*Z*,8*Z*)-11-[*tert*-Butoxycarbonyl-(2-{(*S*)-(5*Z*-8*Z*)-11-[(*tert*-butoxycarbonyl-(2-hydroxyethyl)amino]tetradeca-5,8-dienlyloxy}ethyl)amino]tetradeca-5,8-dienoic Acid (31). To a stirred solution of **28** (17.0 mg, 17.2 μmol) in THF (0.3 mL) was added TBAF (1 M in THF; 20 μl, 20 μmol). At 4 h, the mixture was concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, elution with 29% EtOAc in hexanes containing 1% HOAc) to give 12.1 mg (16.2 μmol, 94%) of **31** as a clear oil: $[\alpha]^{20}_D$ −21.9 (*c* 0.77, CH_2Cl_2); IR (film) 3400 (br), 3100 (br), 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.28−5.47 (m, 8H), 4.13−4.21 (m, 2H), 3.81−4.10 (m, 2H), 3.71−3.75 (m, 2H), 3.20−3.33 (m, 4H), 2.72−2.85 (m, 4H), 2.00−2.38 (m, 12H), 1.61−1.75 (m, 4H), 1.25−1.52 (m, 26 H), 0.94 (t, 6H, J = 7.0 Hz); HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{73}N_2O_9$ $(M + H)^+$ 749.5316, found 749.5302.

(7*Z*,10*Z*,22*Z*,25*Z*)-(5*S*,20*S*)-15,30-Dioxo-5,20-dipropyl-1,-16-dioxa-4,19-diazacyclotriaconta-7,10,22,25-tetraene-4,-19-dicarboxylic Acid Di-*tert*-butyl Ester (34). A mixture

(10) The existence of stable conformers resulted in unsuitable ^{13}C NMR spectra for all Boc-protected intermediates. Attempts to obtain NMR spectra of these compounds in DMSO at elevated temperature led to product decomposition.

of **31** (8.1 mg, 10.8 μmol) and Et_3N (13 μL, 93 μmol) in acetonitrile (2.3 mL) was added to a refluxing solution of 2-chloro-1-methylpyridinium iodide (11.4 mg, 44.6 μmol) in acetonitrile (12 mL) over a period of 2 h via syringe pump. The mixture was refluxed for an additional 0.5 h, then cooled, and concentrated in vacuo. The solid yellow residue was taken up in H_2O and extracted with ether. The organic extract was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 13% EtOAc in hexanes) to give 5.0 mg of **34** (6.8 μmol, 63% yield for cyclization) as a mixture containing approximately 15% of the over-reduced byproduct, which was carried through from the Lindlar reduction, as evidenced by ESI/MS.

Flash chromatography of 2.0 mg of this mixture (silica gel containing 10% silver nitrate, elution with a step gradient from 9% to 50% EtOAc in hexanes, then flushing column with 5% MeOH in CH_2Cl_2) gave 1.4 mg (1.9 μmol) of pure **34** as a clear oil: $[\alpha]^{20}_D$ −30.0 (*c* 0.27, CH_2Cl_2); IR (film) 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.30−5.45 (m, 8H), 4.12−4.20 and 3.83−3.94 (2m, 6H total), 3.18−3.30 (m, 4H), 2.72−2.84 (m, 4H), 2.08−2.35 (m, 12H), 1.67−1.75 (m, 4H), 1.44 and 1.47 (2s, 18H total), 1.26−1.49 (m, 8H), 0.92 (t, 6H, *J* = 7.2 Hz); HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{70}N_2O_8Na$ $(M + Na)^+$ 753.5030, found 753.5004.

(7*Z*,10*Z*,22*Z*,25*Z*)-(5*S*,20*S*)-5,20-Dipropyl-1,16-dioxa-4,-19-diazacyclotriaconta-7,10,22,25-tetraene-15,30-dione (3). To a stirred solution of **34** (1.4 mg, 1.9 μmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added TFA (80 μl, 1.0 mmol). The mixture was brought to room temperature, and stirring was continued. After 45 min the mixture was concentrated under a stream of N_2 to give the TFA salt of **3**. The salt was taken up in H_2O and washed with hexane. The aqueous mixture was basified with 20% aqueous potassium carbonate and extracted with ether. The organic extract was dried (K_2CO_3), filtered, and concentrated in vacuo to give 1.0 mg of **3** (1.9 μmol, 100%) as a clear oil: $[\alpha]^{20}_D$ −6.2 (*c* 0.15, CH_2Cl_2); IR (film) 3008, 1736 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.47−5.53 (m, 2H, 2NCHCH_2-CH=C*H*), 5.41−5.47 (m, 2H, 2C*H*=CHCH_2CH_2CH_2CO_2R), 5.35−5.40 (m, 2H, 2NCHCH_2C*H*=CH), 5.26−5.33 (m, 2H, 2CH=C*H*CH_2CH_2CH_2CO_2R), 4.19 (ddd, 2H, *J* = 11.0, 6.1, 4.4 Hz, 2OC$H_a$$H_bCH_2$N), 4.12 (ddd, 2H, *J* = 11.0, 7.2, 4.4 Hz, 2OC$H_a$$H_bCH_2$N), 2.80−2.91 (m, 4H, 2CH=CHCH_2CH=CH), 2.69 (ddd, 2H, *J* = 12.4, 7.2, 4.4 Hz, 2OCH_2C$H_a$$H_b$N), 2.63 (ddd, 2H, *J* = 12.4, 6.1, 4.4 Hz, 2OCH_2C$H_a$$H_b$N), 2.46 (quin, 2H, *J* = 5.8 Hz, 2NC*H*), 2.20 (t, 4H, *J* = 7.3 Hz, 2CH_2CO_2R), 2.17−2.33 (m, 2H, 2NCHC$H_a$$H_b$CH=CH), 2.13−2.07 (m, 2H, 2NCHC$H_a$$H_b$CH=CH), 2.06 (q, 4H, *J* = 7.3 Hz, 2CH_2CH_2CH_2-CO_2R), 1.66 (quin, 4H, *J* = 7.3 Hz, 2CH_2CH_2CO_2R), 1.19−1.40 (m, 8H, 2CH_2CH_2CH_3), 0.91 (t, 6H, *J* = 6.6 Hz, 2CH_2CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 173.2, 130.8, 129.7, 129.6, 127.7, 64.9, 57.7, 46.4, 37.3, 34.0, 32.9, 27.2, 26.6, 25.5, 19.6, 15.0; HRMS (ESI, *m*/*z*) calcd for $C_{32}H_{55}N_2O_4$ $(M + H)^+$ 531.4162, found 531.4181.

(*S*)-(*Z*)-11-[[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-(dimethylethoxycarbonyl)amino]tetradec-5-enoic Acid Allyl Ester (21). Starting with **20** (33.3 mg, 66.6 μmol) the procedure for **18** was followed to give 30.6 mg (56.7 μmol, 85%) of **21** as a pale yellow oil: $[\alpha]^{20}_D$ +2.1 (*c* 1.11, CH_2Cl_2); IR (film) 1738, 1692 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.92 (ddt, 1H, *J* = 17.0, 10.4, 5.8 Hz), 5.28−5.42 (m, 2H), 5.31 (dq, 1H, *J* = 17.1, 1.5 Hz), 5.23 (dq, 1H, *J* = 10.4, 1.3 Hz), 4.58 (dt, 2H, *J* = 5.7, 1.4 Hz), 3.74−4.07 (m, 1H), 3.69 and 3.62−3.65 (t and m respectively, 2H total, *J* = 6.8 Hz), 3.13 and 3.04−3.08 (t and m respectively, 2H total, *J* = 6.8 Hz), 2.336 and 2.340 (2t, 2H total, *J* = 7.6 Hz), 1.93−2.09 (m, 4H), 1.66−1.73 (m, 2H), 1.44 and 1.46 (2s, 9H total), 1.19−1.42 (m, 10H total), 0.80−0.91 (m, 3H), 0.89 and 0.90 (2s, 9H total), 0.063 and 0.068 (2s, 6H total); HRMS (FAB, *m*/*z*) calcd for $C_{25}H_{50}NO_3Si$ [(M-Boc) + H]$^+$ 440.3560, found 440.3560.

(*S*)-(*Z*)-11-[*tert*-Butoxycarbonyl(2-hydroxyethyl)amino]-tetradec-5-enoic Acid Allyl Ester (22). Starting with **21** (30.6 mg, 56.7 μmol) the procedure for **19** was followed to give 23.0 mg (54.0 μmol, 95%) of **22** as a pale yellow oil: $[\alpha]^{20}_D$ +0.50 (*c* 2.09, CH_2Cl_2); IR (film) 3454 (br), 1740, 1690, 1664 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.92 (ddt, 1H, *J* = 17.1, 10.4, 5.7 Hz), 5.29−5.42 (m, 2H), 5.32 (dq, 1H, *J* = 17.1, 1.5 Hz), 5.23 (dq, 1H, *J* = 10.4, 1.3 Hz), 4.58 (dt, 2H, *J* = 5.7, 1.4 Hz), 3.85−4.10 (m, 1H), 3.71 (t, 2H, *J* = 4.7 Hz), 3.16−3.29 (m, 3H), 2.34 (t, 2H, *J* = 7.5 Hz), 2.07 (q, 2H, *J* = 7.3 Hz), 1.99−2.03 (m, 2H), 1.70 (quin, 2H, *J* = 7.4 Hz), 1.46 (s, 9H), 1.24−1.45 (m, 10H), 0.91 (t, 3H, *J* = 7.0 Hz); HRMS (FAB, *m*/*z*) calcd for $C_{19}H_{36}NO_3$ $(M + H)^+$ 326.2695, found 326.2695.

(*S*)-(*Z*)-11-[*tert*-Butoxycarbonyl-(2-{(*S*)-(*Z*)-11-[[2-(*tert*-butyldimethylsilanyloxy)ethyl](dimethylethoxycarbonyl)-amino]tetradec-5-enlyloxy}ethyl)amino]tetradec-5-enoic Acid Allyl Ester (23). To a stirred solution of **20** (23.6 mg, 47.2 μmol), **22** (17.1 mg, 40.2 μmol), and DMAP (2.5 mg, 20 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added EDCI (8 mg, 40 μmol). The mixture was slowly brought to room temperature, stirred for 3 h, and then concentrated under a stream of N_2. The residue was purified by flash chromatography (silica gel, 6% EtOAc in hexanes) to give 21.9 mg (24.1 μmol, 60%) of **23** as a pale yellow oil: $[\alpha]^{25}_D$ +3.0 (*c* 1.68, CH_2Cl_2); IR (film) 1736, 1692 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.92 (ddt, 1H, *J* = 17.2, 10.4, 5.7 Hz), 5.29−5.42 (m, 4H), 5.32 (dq, 1H, *J* = 17.1, 1.5 Hz), 5.24 (dq, 1H, *J* = 10.4, 1.3 Hz), 4.58 (dt, 2H, *J* = 5.8, 1.4 Hz), 4.17 and 4.14 (2t, 2H total, *J* = 6.9 Hz for both), 3.75−4.09 (m, 2H), 3.70 and 3.62−3.66 (t and m respectively, 2H total, *J* = 7.0 Hz), 3.03−3.31 (m, 4H), 2.27−2.36 (m, 4H), 1.95−2.10 (m, 8H), 1.66−1.73 (m, 4H), 1.446, 1.452, 1.462 and 1.470 (4s, 18H total), 1.20−1.43 (m, 20H), 0.90 and 0.91 (2s, 9H total), 0.88−0.92 (m, 6H), 0.068 and 0.073 (2s, 6H total); HRMS (FAB, *m*/*z*) calcd for $C_{42}H_{79}N_2O_7Si$ [(M-Boc, isobutene) + H]$^+$ 751.5657, found 751.5658.

(*S*)-(*Z*)-11-[*tert*-Butoxycarbonyl-(2-{(*S*)-(*Z*)-11-[[2-(*tert*-butyldimethylsilanyloxy)ethyl](dimethylethoxycarbonyl)-amino]tetradec-5-enlyloxy}ethyl)amino]tetradec-5-enoic Acid (26). Starting with **23** (16.5 mg, 18.2 μmol), the procedure for **28** was followed to give 11.7 mg (13.5 μmol, 74%) of **26** as a pale yellow oil: $[\alpha]^{25}_D$ +2.9 (*c* 1.09, CH_2Cl_2); IR (film) 3192 (br), 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.27−5.43 (m, 4H), 4.14 and 4.18 (2t, 2H total, *J* = 6.7 Hz), 3.78−4.08 (m, 2H), 3.64 and 3.70 (2t, 2H total, *J* = 6.8 and 7.5 Hz respectively), 3.05−3.28 (m, 4H), 2.28−2.37 (m, 4H), 1.96−2.19 (m, 8H), 1.65−1.76 (m, 4H), 1.448, 1.454, 1.464, and 1.482 (4s, 18H total), 1.21−1.43 (m, 20H), 0.90 and 0.91 (2s, 9H total), 0.88−0.93 (m, 6H), 0.070 and 0.074 (2s, 6H total); HRMS (FAB, *m*/*z*) calcd for $C_{43}H_{83}N_2O_7Si$ [(M-Boc) + H]$^+$ 767.5970, found 767.5964.

(*S*)-(*Z*)-11-[*tert*-Butoxycarbonyl(2-{(*S*)-(*Z*)-11-[(*tert*-butoxycarbonyl(2-hydroxyethyl)amino]tetradec-5-enlyloxy}-ethyl)amino]tetradec-5-enoic Acid (29). Starting with **26** (10.2 mg, 11.8 μmol), the procedure for **31** was followed to give 8.0 mg (10 μmol, 90%) of **29** as a pale yellow oil: $[\alpha]^{25}_D$ +1.7 (*c* 0.80, CH_2Cl_2); IR (film) 3446 (br), 3200 (br), 1738, 1686, 1652 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.27−5.43 (m, 4H), 4.15 and 4.18 (2t, 2H total, *J* = 6.7 Hz for both), 3.81−4.09 (m, 2H), 3.72 (t, 2H, *J* = 5.1 Hz), 3.13−3.29 (m, 4H), 2.35 (t, 2H, *J* = 7.0 Hz), 2.28−2.34 (m, 2H), 1.95−2.19 (m, 8H), 1.63−1.76 (m, 4H), 1.46, 1.47, and 1.48 (3s, 18H total), 1.20−1.43 (m, 20H), 0.90 and 0.91 (2t, 6H total, *J* for both = 7.2 Hz); HRMS (FAB, *m*/*z*) calcd for $C_{37}H_{69}N_2O_7$ [(M-Boc) + H]$^+$ 653.5105, found 653.5104.

(10*Z*,25*Z*)-(5*S*,20*S*)-15,30-Dioxo-5,20-dipropyl-1,16-dioxa-4,19-diazacyclotriaconta-10,25-diene-4,19-dicarboxylic Acid Di-*tert*-butyl Ester (32). Starting with **29** (7.1 mg, 9.4 μmol), the procedure for **34** was followed, with the omission of the (silica/silver nitrate) chromatography step, to give 4.1 mg (5.6 μmol, 59%) of **32** as a clear oil: $[\alpha]^{25}_D$ +2.0 (*c* 0.41, CH_2Cl_2); IR (film) 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.29−5.43 (m, 4H), 4.12−4.24 (m, 4H), 3.72−4.08 (m, 2H), 3.13−3.34 (m, 4H), 2.29−2.33 (m, 4H), 1.96−2.09 (m, 8H), 1.65−1.73 (m, 4H), 1.46 and 1.47 (2s, 18H total), 1.20−1.43 (m, 20H), 0.91 (t, 6H, *J* = 7.5 Hz); HRMS (FAB, *m*/*z*) calcd for $C_{33}H_{59}N_2O_6$ [(M-Boc; isobutene) + H]$^+$ 579.4373, found 579.4372.

(10*Z*,25*Z*)-(5*S*,20*S*)-5,20-Dipropyl-1,16-dioxa-4,19-diazacyclotriaconta-10,25-diene-15,30-dione (1). The Boc-protected diene **32** (3.7 mg, 5.0 μmol) was taken up in TFA (100

μl) and allowed to sit for 15 min. The TFA was removed under a stream of N_2, and the residue was taken up in 20% aqueous potassium carbonate and extracted with ether. The organic extract was dried (K_2CO_3), filtered, and concentrated in vacuo to give 2.7 mg (5.0 μmol, 100%) of **1** as a clear oil: $[\alpha]^{25}_D$ +8.5 (*c* 0.25, CH_2Cl_2); IR (film) 3350 (w, br), 1735 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.47 (dtt, 2H, *J* = 10.8, 7.3, 1.5 Hz, 2C*H*=CHCH$_2$CH$_2$CH$_2$CO$_2$R), 5.34 (dtt, 2H, *J* = 10.8, 7.4, 1.5 Hz, 2CH=C*H*CH$_2$CH$_2$CH$_2$CO$_2$R), 4.19 (ddd, 2H, *J* = 11.0, 5.9, 5.0 Hz, 2OC*H*$_a$H$_b$CH$_2$N), 4.14 (ddd, 2H, 11.0, 6.4, 5.0 Hz, 2OCH$_a$*H*$_b$CH$_2$N), 2.63−2.70 (m, 4H, 2OCH$_2$C*H*$_2$N), 2.40−2.44 (m, 2H, 2NC*H*), 2.20 (t, 4H, *J* = 7.3 Hz, 2C*H*$_2$CO$_2$R), 2.05 (q, 8H, *J* = 7.2 Hz, 2C*H*$_2$CH=CHC*H*$_2$), 1.67 (quin, 4H, *J* = 7.3 Hz, 2C*H*$_2$CH$_2$CO$_2$R), 1.23−1.38 (m, 20 H, 2C*H*$_2$C*H*$_2$C*H*$_2$CHNC*H*$_2$C*H*$_2$CH$_3$), 0.92 (t, 6H, *J* = 7.1 Hz, 2CH$_2$C*H*$_3$); ^{13}C NMR (C_6D_6, 100 MHz) δ 172.9, 131.1, 129.1, 64.6, 57.0, 45.6, 37.1, 34.4, 33.6, 30.3, 27.6, 26.9, 25.6, 25.2, 19.2, 14.6; HRMS (FAB, *m*/*z*) calcd for $C_{32}H_{59}N_2O_4$ [(M-Boc) + H)]$^+$ 535.4475, found 535.4477.

(*S*)-(5*Z*,8*Z*)-11-[[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-(dimethylethoxycarbonyl)amino]tetradeca-5,8-dienoic Acid 2-[((*S*)-(*Z*)-10-Allyloxycarbonyl-1-propyldec-6-enyl)-*tert*-butoxycarbonylamino]ethyl Ester (24). Starting with **17** (20.9 mg, 33.6 μmol) and **22** (15.3 mg, 35.9 μmol), the procedure for **25** was followed to give 24.6 mg (23.9 μmol, 71%) of **24** as a pale yellow oil: $[\alpha]^{20}_D$ −5.13 (*c* 2.24, CH_2Cl_2); IR (film) 1738, 1690 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 7.66−7.68 (m, 4H), 7.36−7.45 (m, 6H), 5.92 (ddt, 1H, *J* = 17.2, 10.4, 5.8 Hz), 5.23−5.42 (m, 7H), 5.24 (dq, 1H, *J* = 10.4, 1.3 Hz), 4.58 (dt, 2H, *J* = 5.7, 1.4 Hz), 4.14 and 4.18 (2t, 2H total, *J* = 6.8 Hz for both), 3.83−4.09 (m, 2H), 3.62−3.80 (m, 2H), 3.13−3.31 (m, 4H), 2.64−2.77 (m, 2H), 2.34 (t, 2H, *J* = 7.6 Hz), 2.28−2.35 (m, 2H), 1.94−2.17 (m, 8H), 1.66−1.74 (m, 4H), 1.36, 1.43, 1.46 and 1.47 (4s, 18H total), 1.17−1.45 (m, 14H), 1.05 (s, 9H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.80−0.85 (m, 3H); HRMS (ESI, *m*/*z*) calcd for $C_{61}H_{97}N_2O_9Si$ (M + H)$^+$ 1029.6963, found 1029.6894.

(*S*)-(5*Z*,8*Z*)-11-[[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-(dimethylethoxycarbonyl)amino]tetradeca-5,8-dienoic Acid 2-[*tert*-Butoxycarbonyl-((*S*)-(*Z*)-10-carboxy-1-propyldec-6-enyl)amino]ethyl Ester (27). Starting with **24** (24.6 mg, 23.9 μmol), the procedure for **28** was followed to give 22.0 mg (22.2 μmol, 93%) of **27** as a pale yellow oil: $[\alpha]^{20}_D$ −5.2 (*c* 1.81, CH_2Cl_2); IR (film) 3200 (br), 1738, 1694 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 400 MHz) δ 7.65−7.69 (m, 4H), 7.36−7.46 (m, 6H), 5.23−5.43 (m, 6H), 4.15 and 4.19 (2t, 2H total, *J* = 6.7 Hz for both), 3.62−4.09 (m, 4H), 3.09−3.31 (m, 4H), 2.64−2.78 (m, 2H), 2.35 (t, 2H, *J* = 7.3 Hz), 2.27−2.34 (m, 2H), 1.92−2.20 (m, 8H), 1.66−1.76 (m, 4H), 1.36, 1.43, 1.46 and 1.48 (4s, 18H total), 1.16−1.48 (m, 14H), 1.05 (s, 9H), 0.88−0.93 (m, 3H), 0.80−0.85 (m, 3H); HRMS (ESI, *m*/*z*) calcd for $C_{58}H_{92}N_2O_9Si$ (M + H)$^+$ 989.6650, found 989.6640.

(*S*)-(5*Z*,8*Z*)-11-[*tert*-Butoxycarbonyl-(2-hydroxyethyl)-amino]tetradeca-5,8-dienoic Acid 2-[*tert*-Butoxycarbonyl-((*S*)-(*Z*)-10-carboxy-1-propyldec-6-enyl)amino]ethyl Ester (30). Starting with **27** (21.1 mg, 21.3 μmol), the procedure for **31** was followed to give 14.2 mg (18.9 μmol, 89%) of **30** as a pale yellow oil: $[\alpha]^{20}_D$ −8.1 (*c* 1.23, CH_2Cl_2); IR (film) 3432 (br), 3200 (br), 1738, 1690 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.26−5.45 (m, 6H), 4.13−4.20 (m, 2H), 3.71−4.10 (m, 4H), 3.15−3.32 (m, 4H), 2.77 (t, 2H, *J* = 5.7 Hz), 1.96−2.37 (m, 12H), 1.66−1.76 (m, 4H), 1.46, 1.47 and 1.48 (3s, 18H total), 1.23−1.51 (m, 14H), 0.89−0.94 (m, 6H); HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{74}N_2O_9$ (M + H)$^+$ 751.5473, found 751.5463.

(10*Z*,22*Z*25*Z*)-(5*S*,20*S*)-15,30-Dioxo-5,20-dipropyl-1,16-dioxa-4,19-diazacyclotriaconta-10,22,25-triene-4,19-dicarboxylic Acid Di-*tert*-butyl Ester (33). Starting with **30** (14.3 mg, 19.0 μmol), the procedure for **34** was followed until the crude residue from the ether extraction was obtained. The residue was purified by flash chromatography (silica gel containing 10% silver nitrate by mass, elution with a step gradient from 33% to 50% EtOAc in hexanes) to give 6.4 mg (8.7 μmol, 46%) of **33** as a clear oil: $[\alpha]^{20}_D$ −1.1 (*c* 0.49, CH_2Cl_2); IR (film) 1736, 1690 cm^{-1}; ^1H NMR (conformeric mixture, $CDCl_3$, 500 MHz) δ 5.28−5.43 (m, 6H), 4.09−4.25 (m, 4H), 3.71−4.09 (m, 2H), 3.12−3.37 (m, 4H), 2.78 (t, 2H, *J* = 5.9 Hz), 2.22−2.36 (m, 6H), 1.99−2.14 (m, 6H), 1.64−1.75 (m, 4H), 1.22−1.52 (m, 32H), 0.091 and 0.092 (2t, 6H, *J* = 7.4 Hz for both); HRMS (ESI, *m*/*z*) calcd for $C_{42}H_{73}N_2O_8$ (M + H)$^+$ 733.5367, found 733.5381.

(10*Z*,22*Z*,25*Z*)-(5*S*,20*S*)-5,20-Dipropyl-1,16-dioxa-4,19-diazacyclotriaconta-10,22,25-triene-15,30-dione (2). Starting with **33** (5.4 mg, 7.4 μmol), the procedure for **3** was followed to give 3.5 mg (6.6 μmol, 89%) of **2** as a clear oil: $[\alpha]^{20}_D$ −0.09 (*c* 0.32, CH_2Cl_2); IR (film) 3324 (w, br), 1736 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 5.29−5.57 (m, 6H, 3C*H*=C*H*), 4.09−4.21 (m, 4H, 2OC*H*$_2$CH$_2$N), 2.79−2.91 (m, 2H, CH=CHC*H*$_2$CH=CH), 2.61−2.73 (m, 4H, 2OCH$_2$C*H*$_2$N), 2.40−2.49 (m, 2H, 2NC*H*), 2.21 (t, 2H, *J* = 7.2 Hz, C*H*$_2$CO$_2$R), 2.20 (t, 2H, *J* = 7.2 Hz, C*H*$_2$CO$_2$R), 2.17−2.23 (m, 1H, NCHC*H*$_a$H$_b$CH=CH), 2.08−2.14 (m, 1H, NCHCH$_a$*H*$_b$CH=CH), 2.06 (q, 6H, *J* = 7.3 Hz, CH$_2$C*H*$_2$CH=CHC*H*$_2$CH$_2$ and C*H*$_2$CH=CHCH$_2$CH=CHCH$_2$CHN), 1.63−1.70 (m, 4H, 2C*H*$_2$CH$_2$CO$_2$R), 1.20−1.40 (m, 14H, C*H*$_2$C*H*$_2$C*H*$_2$CHN and 2C*H*$_2$C*H*$_2$CH$_3$), 0.92 (t, 3H, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 0.91 (t, 3H, *J* = 6.8 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (C_6D_6, 100 MHz) δ 173.29, 173.27, 131.5, 130.7, 129.7, 129.6, 129.5, 127.7, 65.03, 64.93, 57.7, 57.4, 46.4, 46.0, 37.5, 37.3, 34.7, 34.02, 34.01, 32.9, 30.7, 28.0, 27.28, 27.26, 26.6, 25.9, 25.6, 25.5, 19.7, 19.6, 15.04, 15.00; HRMS (ESI, *m*/*z*) calcd for $C_{32}H_{57}N_2O_4$ (M + H)$^+$ 533.4318, found 533.4286.

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Supporting Information Available: ^1H NMR spectra of all synthesized compounds and ^{13}C NMR spectra of compounds **1**−**3**, **9**−**11**, and **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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