Articles

Conformationally Constrained [*p*-(ω-Aminoalkyl)phenacetyl]-L-seryl-L-lysyl Dipeptide Amides as Potent Peptidomimetic Inhibitors of *Candida albicans* and Human Myristoyl-CoA:Protein *N*-Myristoyl Transferase

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MyristoylCoA:protein *N*-myristoyltransferase (NMT) covalently attaches the 14-carbon saturated fatty acid myristate, via an amide bond, to the N-terminal glycine residues of a variety of cellular proteins. Genetic studies have shown that NMT is essential for the viability of the principal fungal pathogens which cause systemic infection in immunosuppressed humans and hence is a target for development of fungicidal drugs. We have generated a class of potent peptidomimetic inhibitors of the NMT from one such fungal pathogen, *Candida albicans*. The N-terminal tetrapeptide from a substrate analog inhibitor, ALYASKL-NH_2, was replaced with an ω-aminoalkanoyl moiety having an optimal 11-carbon chain for inhibition (11-aminoundecanoyl-SKL-NH_2, **3a**, $IC_{50} = 1.2 \pm 0.14$ μM). A series of replacements for the C-terminal Leu established that residues containing a lipophilic side chain were most effective, with cyclohexylalanine having the greatest potency (**3g**, $IC_{50} = 0.36 \pm 0.06$ μM). Removal of the carboxamide moiety led to a metabolically stable dipeptide inhibitor containing an *N*-(cyclohexylethyl)lysinamide (**17e**, $IC_{50} = 0.11 \pm 0.03$ μM). Partial rigidification of the flexible aminoundecanoyl chain produced the dipeptide *p*-(ω-aminohexyl)phenacetyl-L-seryl-L-lysyl-*N*-(cyclohexylethyl)amide (**26b**, $IC_{50} = 0.11 \pm 0.04$ μM). Subsequent incorporation of an α-methyl substituent into **26b** provided the dipeptide analog [2-[*p*-(ω-aminohexyl)phenyl]propionyl]-L-seryl-L-lysyl-*N*-(cyclohexylethyl)amide, a very potent inhibitor (**48**, $IC_{50} = 0.043 \pm 0.006$ μM), which retained the three essential elements required for recognition by the acyl transferase's peptide binding site.

Introduction

MyristoylCoA:protein *N*-myristoyltransferase (NMT; EC 2.1.3.97) is a cytosolic monomeric enzyme which catalyzes the transfer of a rare cellular fatty acid, myristate (C14:0), from myristoylCoA to the N-terminal glycine amine of a variety of eukaryotic proteins.[1] These protein substrates include kinases, phosphatases, and other molecules involved in intracellular signal transduction cascades. The covalent attachment of C14:0 occurs during, not after, synthesis of these substrates and appears to be irreversible. Myristate is used by different *N*-myristoyl proteins for different purposes, although promotion of protein−protein and protein−lipid interactions appear to be common themes.[2]

NMT is a target for development of novel antiviral and antifungal agents. Protein *N*-myristoylation is required for the replication of both enveloped and nonenveloped viruses, including human immunodeficiency virus-1.[3,4] Recent genetic studies using temperature sensitive NMT alleles have shown that the two principal fungal pathogens that cause systemic infections in AIDS patients, *Candida albicans* and *Cryptococcus neoformans*, require NMT to maintain their viability in culture and in vivo.[5,6]

NMT has no obvious sequence similarities to any known proteins. The functional properties of the acyl-CoA binding sites of fungal and human NMT are highly conserved. Potent analog inhibitors of myristoylCoA have been identified.[7] In contrast, the orthologous fungal and human enzymes exhibit distinct differences in their peptide substrate specificities,[8a] raising the possibility that this site can be used for development of selective fungicidal inhibitors. This difference in peptide specificity has recently been exploited to produce the first octapeptide[8b] and dipeptide[8c] inhibitors of NMT.

C. albicans produces a single NMT that acylates <10 proteins which are identifiable by metabolic labeling with [^{3}H]myristate during exponential growth in rich media.[9] An ADP ribosylation factor (Arf) involved in intracellular protein and vesicular trafficking is included among these substrates.[9] An octapeptide (GLYASKLS-NH_2), derived from an N-terminal Arf sequence,[10] has been used recently as the starting point to identify elements critical for recognition by the acyl transferase's peptide binding site. Systematic replacement of each of the amino acid residues in this octapeptide with alanine indicated that there are three key

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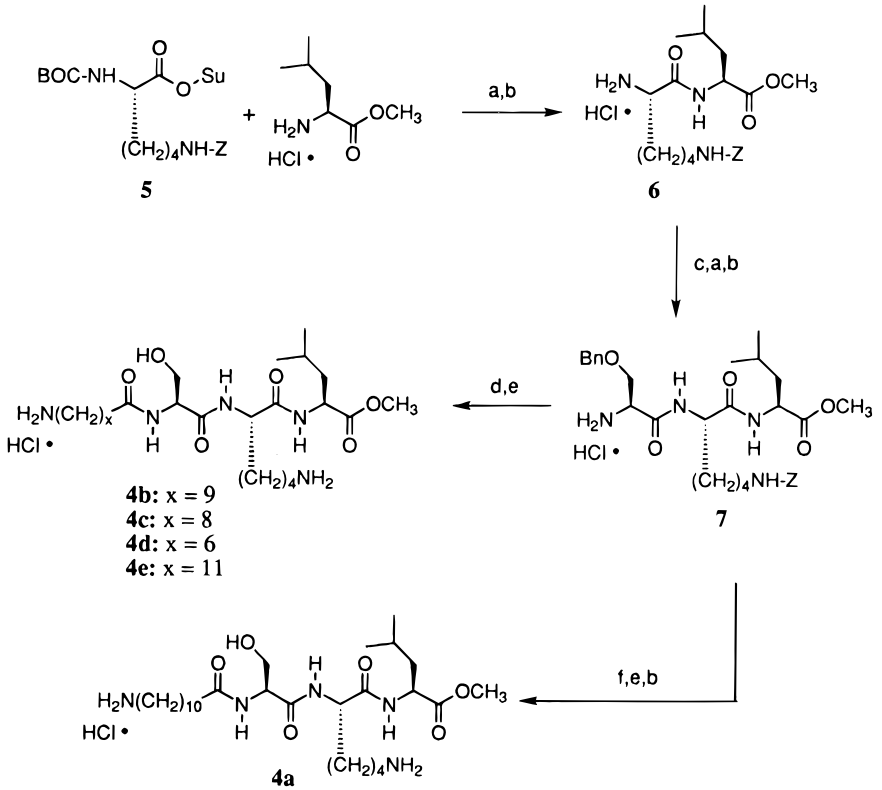
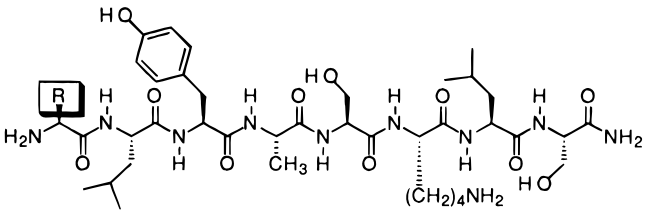
Scheme 1. Synthesis of *N*-(*ω*-Aminoalkanoyl)Tripeptide Esters **4a**−**e**[a]



[a] Reagents: (a) Et_3N; (b) HCl, dioxane; (c) BOC-NHCH-(CH_2OBn)COOSu; (d) $N_3(CH_2)_xCO_2H$, EDC, HOBt, Et_3N; (e) Pd/C, H_2; (f) $BOCNH(CH_2)_{10}CO_2H$, DCC, HOBt, Et_3N.

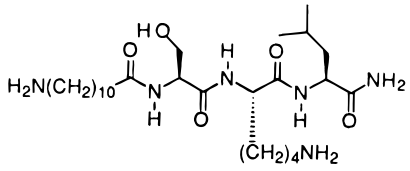
recognition elements required for high-affinity binding by the fungal NMT: the N-terminal amino group of glycine-1, the hydroxyl group of serine-5, and the ϵ-amino group of lysine-6. Moreover, the substitution of alanine for glycine yielded the first competitive inhibitor for the acyl transferase's peptide binding site (ALYASKLS-NH_2; $K_{i(app)} = 15.3 \pm 6.4$ μM).[11]



1 GLYASKLS-NH_2 R = H
2 ALYASKLS-NH_2 R = CH_3

Subsequent modifications of this octapeptide—replacement of the first four amino acids (ALYA) with an 11-aminoundecanoyl moiety and removal of the C-terminal serine carboxamide—produced a more potent, truncated tripeptide amide, **3a** ($IC_{50} = 1.2 \pm 0.14$ μM).[11] The tripeptide maintained the L-seryl-L-lysyl dipeptide that was so critical for the recognition of the parental octapeptide inhibitor. The 11-aminoundecanoyl backbone in **3a** presumably helped maintain the correct binding distance between this dipeptide and the *ω*-amino group.

In the current study, we have explored these distance relationships further and have developed considerably more potent general NMT inhibitors through rigidification of the aminoalkanoyl chain plus modification of the C-terminal residue.

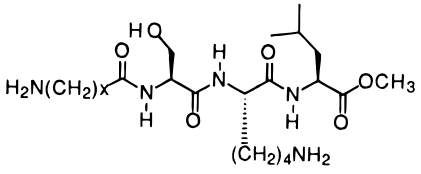


3a

Results and Discussion

Chemistry. Synthetic modifications of **3a** initially focused on defining the optimal length of the alkanoyl chain that connected the N-terminal *ω*-amino group to the Ser-Lys-Leu tripeptide. We then explored the importance of basicity of the N-terminal amino group for recognition. At the C-terminus, further depeptidization of **3a** produced a series of active Ser-Lys dipeptide carboxamides containing lipophilic substituents. Having optimized both ends of the molecule, we then introduced a series of conformational constraints into the flexible *ω*-aminoalkanoyl chain which markedly enhanced potency.

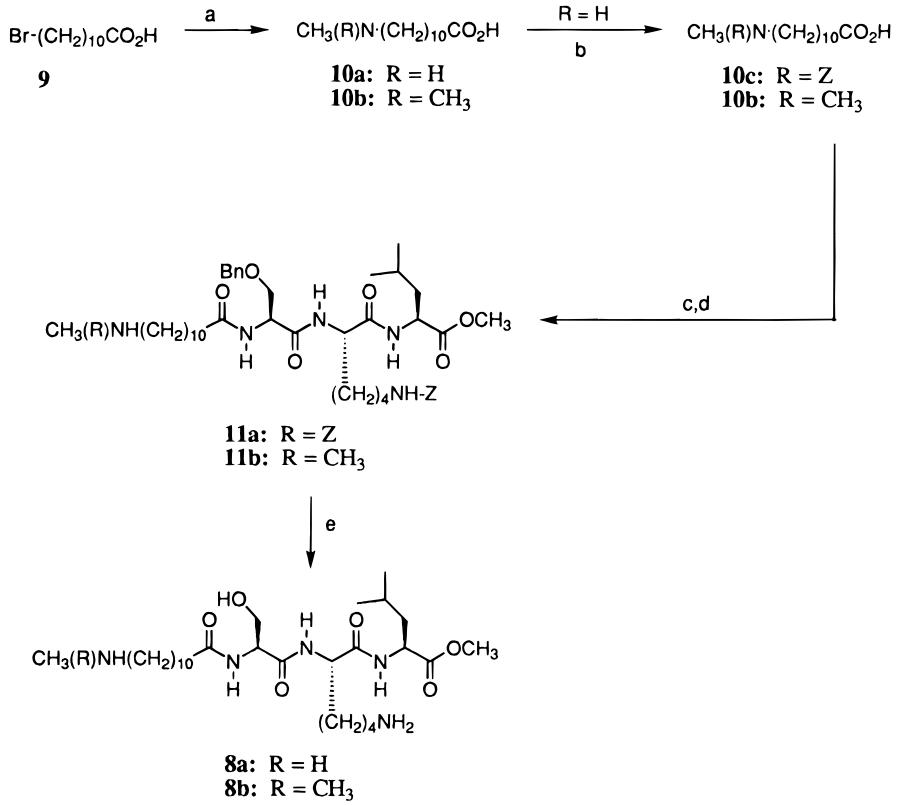
Tripeptide N-Terminal Chain Length Variations. The chain length was systematically altered in a series of tripeptide methyl esters **4a**−**e**, which could be readily prepared by conventional solution-based peptide chemistry, as outlined in Scheme 1.



4a-e

The differentially protected lysine *N*-hydroxysuccinimide (OSu)[12] ester **5** was treated with leucine methyl

Scheme 2. Synthesis of *N*-(Methylaminoundecanoyl) and *N*,*N*-(Dimethylaminoundecanoyl)Tripeptide Esters **8a,b**[a]



[a] Reagents: (a) $CH_3(R)NH$, MeOH, room temperature; (b) Z-Cl, Et_3N; (c) EDC, HOBt, Et_3N; (d) **7**; (e) Pd/C, H_2.

ester hydrochloride and triethylamine to give the ϵ-*N*-Z protected Lys-Leu dipeptide ester hydrochloride **6**, after removal of the *N*-BOC protecting group with hydrochloric acid. Subsequent coupling with the *N*-hydroxysuccinimide ester of *N*-BOC-*O*-Bn-L-serine and removal of the *N*-BOC protecting group produced the protected Ser-Lys-Leu tripeptide ester hydrochloride **7**, which was then coupled with either 11-(*N*-BOC-amino)undecanoic acid[13] or the appropriate ω-azido aliphatic acid.[14] The *N*-BOC protecting group was removed with hydrochloric acid. Final deprotection and reduction of the azido group were accomplished simultaneously using hydrogen over palladium on carbon to give **4a**−**e**, after purification by HPLC.

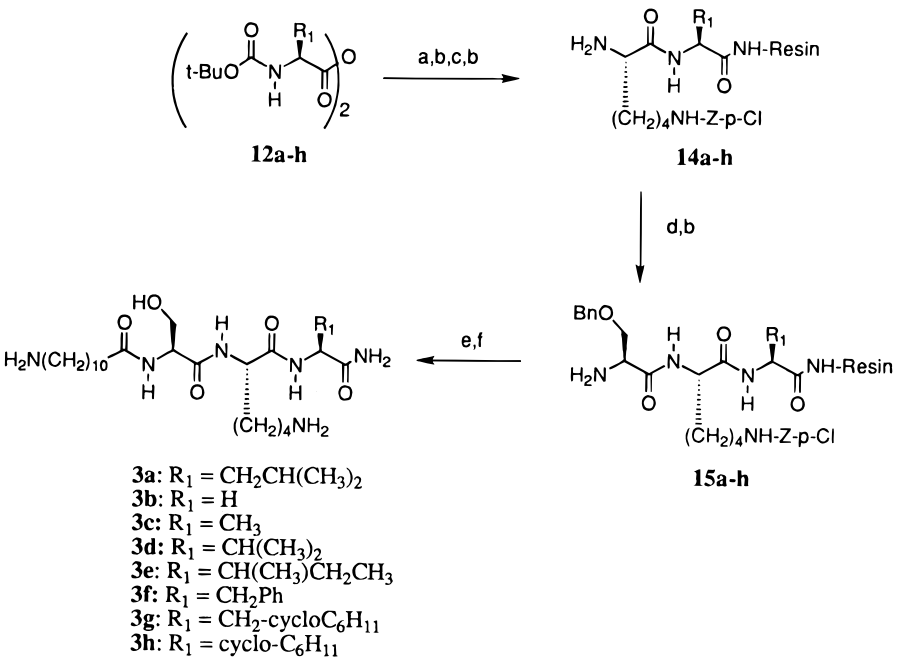
***N*-Alkyl Terminal Amine Substituents.** Two *N*-alkylated analogs of **4a** were prepared that incorporated an *N*-methylamino moiety **8a** and an *N*,*N*-dimethylamino group **8b**, as outlined in Scheme 2. The appropriate 11-(*N*-methylamino)- (**10a**) and 11-(*N*,*N*-dimethylamino)- (**10b**) undecanoic acids were synthesized from commercially available 11-bromoundecanoic acid **9**, as outlined in Scheme 6. The secondary amine was further protected as the *N*-Z derivative **10c**. After activation with EDC and HOBt, subsequent coupling to the tripeptide Ser-Lys-Leu methyl ester **7** gave the protected tripeptide ester derivatives **11a**,**b**. The final deprotection was accomplished using catalytic hydrogenation over palladium on carbon to afford the desired products **8a**,**b**.

C-Terminus Variations. A series of tripeptides **3a**−**h** were prepared by solid-phase methods (Scheme 3). These solid-phase syntheses began with the desired *N*-BOC-protected amino acids, which were activated as their symmetrical anhydrides **12a**−**h** and then coupled to 4-methylbenzhydrylamine[15] (mBHA) resin **13**. Subsequent removal of the *N*-BOC protecting group from the coupled product, addition of the symmetrical anhydride of *N*-BOC-*N*-ϵ-(*p*-chloro-Z)-L-lysine, and removal of the *N*-BOC protecting group with trifluoroacetic acid produced the desired L-lysyl dipeptides **14a**−**h**. Addition of the symmetrical anhydride of *N*-BOC-*O*-Bn-L-serine and removal of the *N*-BOC protecting group with trifluoroacetic acid afforded the desired protected tripeptides **15a**−**h**. The symmetrical anhydride of *N*-BOC-11-aminoundecanoic acid[13] was then coupled to **15a**−**h**. Final deprotection and cleavage from the resin were accomplished by treatment with hydrofluoric acid with anisole as the scavenger. The tripeptide derivatives **3a**−**h** were purified by reverse-phase chromatography and characterized by spectroscopic techniques as well as by amino acid analyses.

The enantiomer **3a′** was prepared by similar methods described for **3a** using D-serine and D-lysine in place of the L-amino acids. The carboxylic acid derivative **16** related to **3a** was prepared using similar solid-phase methods as described for **3a**−**h**, except *N*-BOC-Leu-OCH_3-Pam-resin was utilized instead of the 4-methylbenzhydrylamine resin and *N*-BOC-Leu.

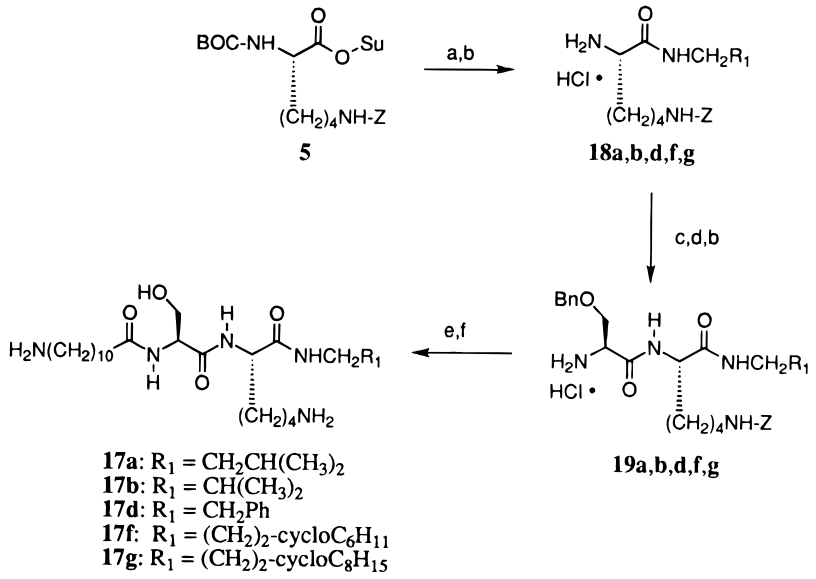
The corresponding dipeptides **17a**−**g** were prepared by several complementary solution methods, as summarized in Schemes 4−6. Installation of the desired amide moiety could be accomplished either early in the sequence (Scheme 4) or at the end (Scheme 5), if desired. As shown in Scheme 4, the differentially protected lysine *N*-hydroxysuccinimide ester **5** was treated with the required primary amine to give the Z-protected lysinamide hydrochlorides **18a**,**b**,**d**,**f**,**g** after removal of the *N*-BOC protecting group with hydrochloric acid. Subsequent coupling with the *N*-hydroxysuccinimide ester of *N*-BOC-*O*-Bn-L-serine and removal of the *N*-BOC protecting group produced the Ser-Lys dipeptide amide hydrochlorides **19a**,**b**,**d**,**f**,**g** which were then coupled

Scheme 3. Solid-Phase Synthesis of Tripeptides **3a**−**h**[a]



[a] Reagents: (a) $NH_2CH(Bn)$-Ph-resin **13**; (b) TFA, CH_2Cl_2, DIEA; (c) [N-BOC-NHCH{$(CH_2)_4NHZ$}CO]$_2$O; (d) [BOC-NHCH(CH_2OBn)CO]$_2$O; (e) [BOC-NH$(CH_2)_{10}$CO]$_2$O; (f) HF.

Scheme 4. Synthesis of Dipeptide Amides **17a,b,d,f,g**[a]



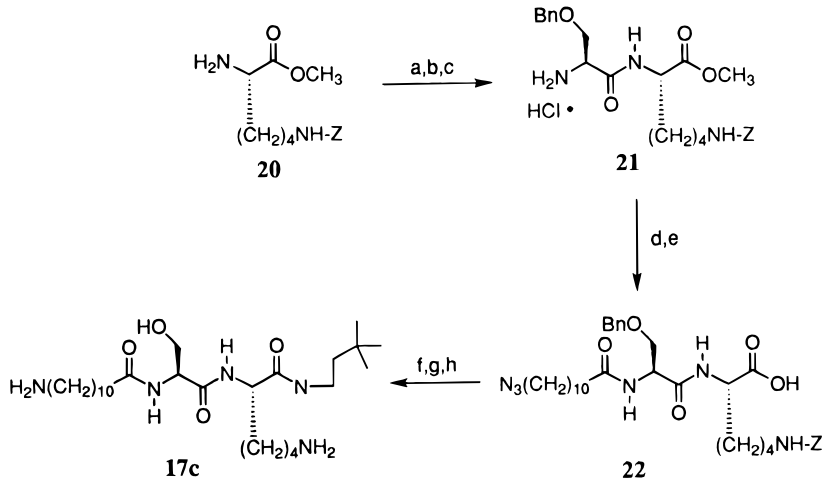
[a] Reagents: (a) $R_1CH_2NH_2$; (b) HCl/dioxane; (c) N-BOC-NHCH(CH_2OBn)CO_2Su; (d) Et_3N; (e) $N_3(CH_2)_{10}CO_2H$, EDC, HOBt, Et_3N; (f) Pd/C, H_2.

with 11-azidoundecanoic acid.[14] Final deprotection and reduction of the azido group were accomplished simultaneously using hydrogen over palladium on carbon to yield the desired dipeptide amides **17a**,**b**,**d**,**f**,**g**, after purification by HPLC. The enantiomer **17a′** was prepared by similar methods described for **17a** using D-serine and D-lysine intermediates in place of the L-amino acids.

Alternatively, as shown in Scheme 5, the protected ϵ-Z-lysine methyl ester **20** was coupled with the *N*-hydroxysuccinimide ester of *N*-BOC-*O*-Bn-L-serine, and the *N*-BOC protecting group was removed to give the protected Ser-Lys dipeptide methyl ester hydrochloride **21**. Subsequent coupling with 11-azido undecanoic acid[14] and basic hydrolysis of the ester produced the protected azidocarboxylic acid **22**, after acidification. The desired amide moiety was then introduced following activation with *N*-hydroxybenzotriazole (HOBt) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (EDC), and subsequent reaction with the 4,4-dimethylbutylamine gave the desired amide **17c**, after deprotection and simultaneous azide reduction using hydrogenolysis.

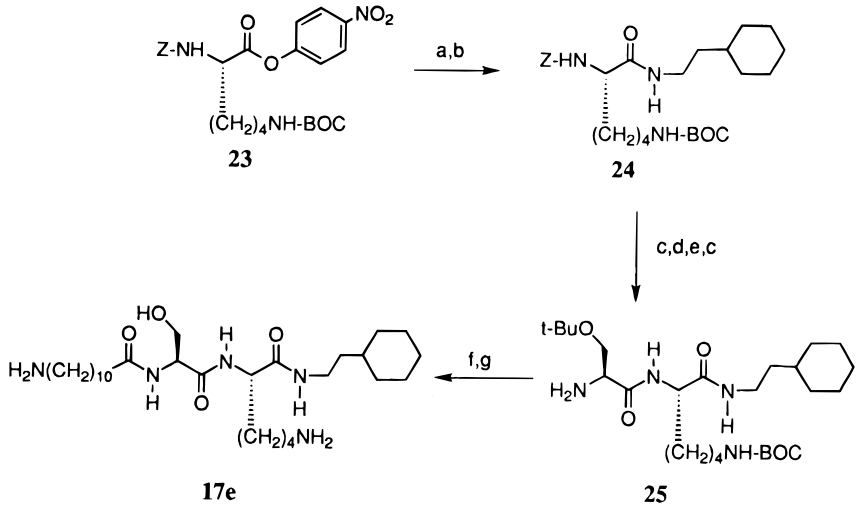
The *N*-cyclohexylethyl dipeptide amide **17e** was conveniently prepared using the sequence outlined in Scheme 6. The commercially available and differentially protected lysine *p*-nitrophenyl ester **23** was treated with cyclohexylethylamine to give the α-Z-ϵ-BOC-lysinamide **24**. Subsequent hydrogenolysis over palladium on carbon, coupling with *N*-Z-*O*-t-Bu-L-serine, and removal of the *N*-Z protecting group gave the protected Ser-Lys dipeptide amide **25**, which was then coupled with the activated ester of 11-(*N*-BOC-amino)undecanoic acid.[13] Final deprotection was accomplished with

Scheme 5. Synthesis of Dipeptide Amide **17c**[a]



[a] Reagents: (a) BOC-NHCH(CH_2OBn)COOSu; (b) Et_3N; (c) HCl, dioxane; (d) $N_3(CH_2)_{10}CO_2H$, EDC, HOBt, Et_3N; (e) LiOH, HCl; (f) EDC, HOBt; (g) $(CH_3)_3CCH_2CH_2NH_2$; (h) Pd/C, H_2.

Scheme 6. Synthesis of Dipeptide Amide **17e**[a]

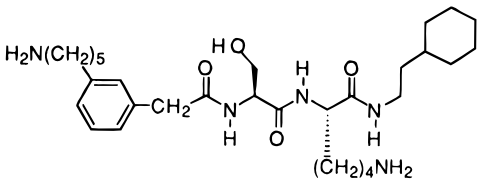


[a] Reagents: (a) HOBt, DMA; (b) cyclohexylethylamine; (c) 5% Pd/C, H_2; (d) Z-NHCH-(CH_2O-*t*-Bu)CO_2H; (e) DCC, HOBt; (f) N-BOC-$NH(CH_2)_{10}CO_2H$, DCC, HOBt, Et_3N; (g) TFA.

trifluoroacetic acid to give the desired *N*-(cyclohexylethyl)lysinamide dipeptide **17e**.

Conformationally Constrained Undecanoyl Chains. Phenylene groups were inserted at specific sites within the 11-aminoundecanoyl group of **17e** in order to rigidify this flexible hydrocarbon chain. A convenient synthesis of a series of *p*-(*ω*-aminoalkyl)-phenylacetamide analogs **26a**−**c** was developed from commercially available *p*-iodophenylacetic acid, as shown in Scheme 7. First, *p*-iodophenylacetic acid **27** was converted to the known[16] methyl ester **28a**, which was then coupled with the appropriate 1-alkynol using palladium catalysis.[8c,18] The resulting unsaturated alcohols **29a**−**c** were reduced by hydrogenation to the saturated alcohols **30a**−**c**, which were then converted to the corresponding azides **32a**−**c** via the iodides **31a**−**c**. The azides were reduced to amines using hydrogen over palladium on carbon. The amines were protected as their *N*-*tert*-butylcarbamates[19] **33a**−**c**, and the esters were hydrolyzed in base to afford the desired carboxylic acids **34a**−**c**, after acidification. Using this procedure, phenylacetic acid analogs containing *p*-aminoalkyl substituents of varying chain length were synthesized. The various acids were then activated and coupled to the previously described *N*-(cyclohexylethyl)amide of the protected Ser-Lys dipeptide **25** to yield the protected intermediates **35a**−**c**. Final deprotection was accomplished with trifluoroacetic acid to afford the desired products **26a**−**c**, after purification by reverse-phase HPLC.

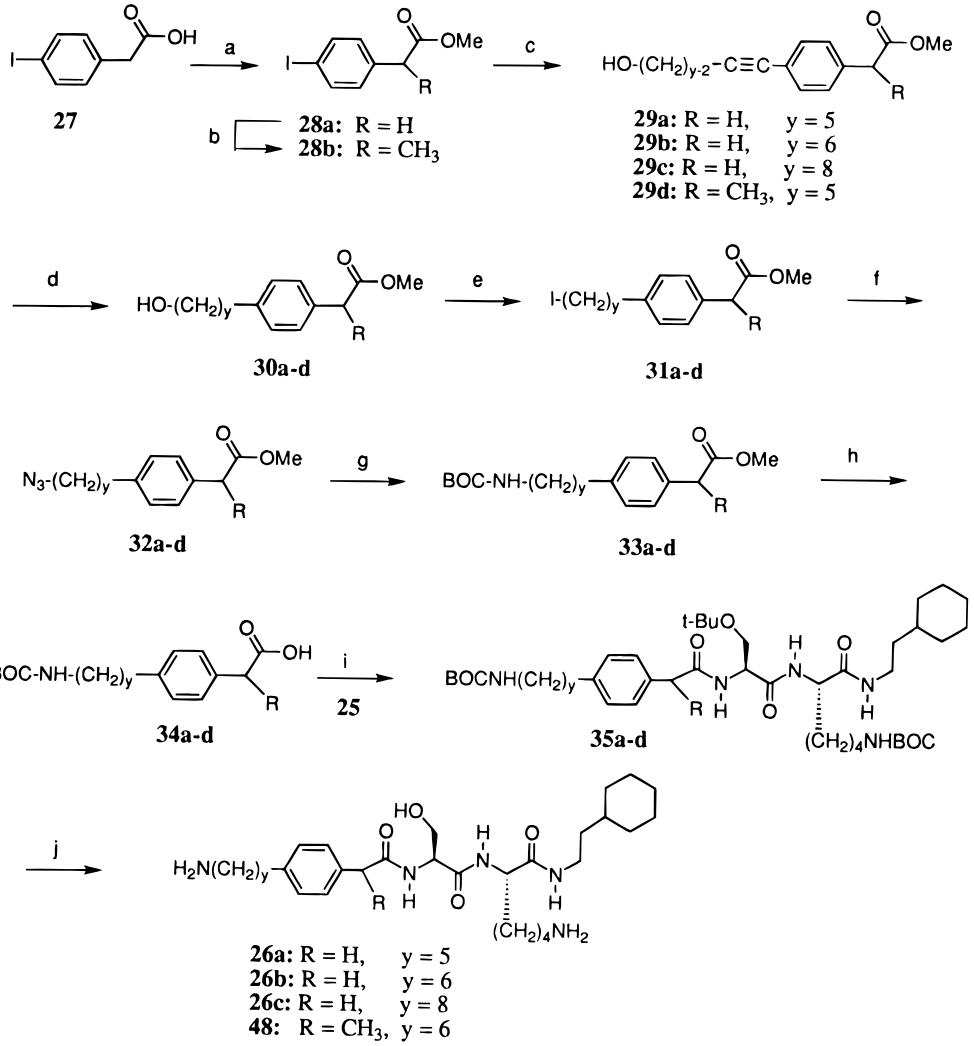
The corresponding *meta*−substituted isomer **36** was prepared by similar methods as outlined in Scheme 7 starting from *m*-iodophenylacetic acid.



36

A complementary series was also prepared which inserted the phenyl ring closer to the N-terminus of the undecanoyl chain. Both the acetylene **37** and its reduced product **38** were prepared by a similar sequence, as outlined in Scheme 8. Commercially available *p*-iodobenzylamine **39** was first *N*-BOC protected[19] to give **40**, which was then coupled with 6-heptynoic acid using palladium catalysis[18] to give the unsaturated 7-[*p*-

Scheme 7. Synthesis of *p*-(ω-Aminoalkyl)phenylacetamides **26a**−**c** and 2-[*p*-(ω-Aminoalkyl)phenyl]propionamide **48**[a]



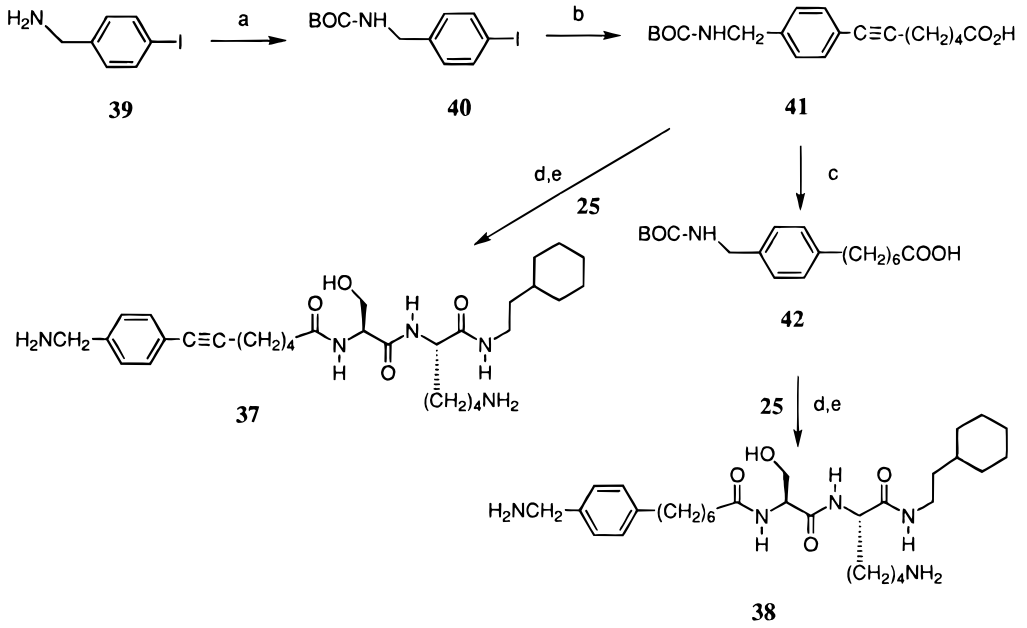
[a] Reagents: (a) 4 N HCl/dioxane, MeOH, room temperature, 16 h; (b) NaH, THF, CH_3I; (c) HO-$(CH_2)_{y-2}$CCH, $(PPh_3)_2PdCl_2$, Et_3N, CuI, CH_3CN, room temperature, 3 h; (d) H_2, Pd/C (5%), 40 psi, room temperature, 4 h; (e) $(PhO)_3PMeI$, CH_3CN, room temperature, 4 h; (f) NaN_3, DMF, room temperature, 16 h; (g) H_2, 5% Pd/C, 40 psi, 3 h, EtOAc, $(BOC)_2O$; (h) 1 M LiOH, MeOH−H_2O, room temperature, 2.5 h; (i) DCC/HOBt, DMF + **25**; (j) trifluoroacetic acid, 3 h.

(*N*-BOC-aminomethyl)phenyl]hept-6-ynoic acid (**41**). This acid was activated and coupled with the previously described protected *N*-(cyclohexylethyl)amide of the Ser-Lys dipeptide **25**. Final deprotection was accomplished with trifluoroacetic acid to afford the desired acetylene product **37**, after purification by reverse-phase HPLC. Alternatively, **41** was hydrogenated to give the saturated 7-[*p*-(*N*-BOC-aminomethyl)phenyl]heptanoic acid (**42**), which also was activated and coupled with the previously described *N*-(cyclohexylethyl)amide of the protected Ser-Lys dipeptide **25**. Removal of the remaining protecting groups was accomplished with trifluoroacetic acid to give the reduced adduct **38**.

Additional rigidifying elements were introduced with the diphenylacetylene analog **43**. As shown in Scheme 9, the syntheses of **43** and **44** began with the previously described[16] methyl *p*-iodophenylacetate **28a**. Palladium-catalyzed[18] cross-coupling with (trimethylsilyl)acetylene produced the terminal acetylene product **45**, after removal of the trimethylsilyl group with tetrabutylammonium fluoride in acetonitrile. Subsequent cross-coupling with the *N*-BOC-protected *p*-iodobenzylamine **40** gave the unsymmetrical diphenylacetylene as the carboxylic acid **46**, after basic hydrolysis and acidification. Compound **46** was then activated and coupled with the previously described *N*-(cyclohexylethyl)amide of the protected Ser-Lys dipeptide **25**. Removal of the remaining protecting groups was accomplished with trifluoroacetic acid to give **43**. Alternatively, compound **46** was hydrogenated over palladium on carbon to give the reduced diphenylethane derivative **47**, which could be activated and coupled with the previously described *N*-(cyclohexylethyl)amide of the protected Ser-Lys dipeptide **25**. Removal of the remaining protecting groups was again accomplished with trifluoroacetic acid to give **44**.

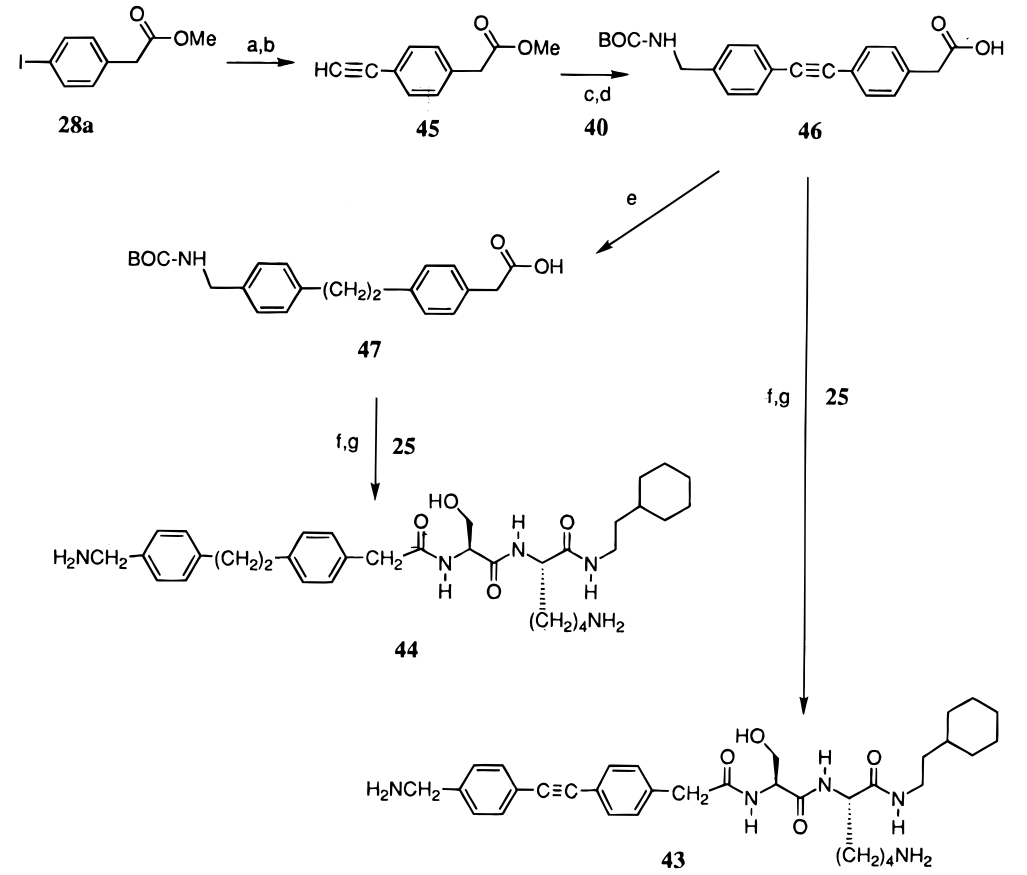
Finally, the synthesis of **48** (Scheme 7) began with the α-alkylation[17] of methyl *p*-iodophenylacetate **28a** with methyl iodide in the presence of NaH in THF to afford racemic methyl (*R,S*)-2-(*p*-iodophenyl)propionate **28b**. This ester was then coupled[17,18] with 5-hexyn-1-ol using catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in the presence of triethylamine, and the resulting product was subjected to catalytic hydrogenation to afford the ω-hydroxy ester **30d**. The reaction of **30d** with methyl triphenoxyphosphonium iodide provided the iodo ester **31d**. Azide displacement on **31d** and hydrogenation followed by *N*-BOC protection[19] produced the *N*-BOC-protected amino ester **33d**, which was saponified in base and acidified to give the corresponding carboxylic acid **34d**. Activation and coupling of **34d** to the previously described *N*-(cyclohexylethyl)amide of the protected Ser-

Scheme 8. Synthesis of [*p*-(Aminomethyl)phenyl]heptanamide (**37**) and 7-[*p*-(Aminomethyl)phenyl]hept-6-ynamide (**38**)[a]



[a] Reagents: (a) $(BOC)_2O$, CH_2Cl_2, room temperature, 16 h; (b) HCC-$(CH_2)_4CO_2H$, $(PPH_3)_2PdCl_2$, Et_3N, CuI, CH_3CN, room temperature, 4 h; (c) H_2, 5% Pd/C, 40, psi, room temperature, 3.5 h; (d) DCC/HOBt, DMF, CH_2Cl_2, **25**, room temperature, 48 h; (e) TFA, room temperature, 3 h.

Scheme 9. Synthesis of *p*-[[*p*-(Aminomethyl)phenyl]ethynyl]phenylacetamide (**43**) and *p*-[[*p*-(Aminomethyl)phenyl]ethyl]phenylacetamide (**44**)[a]



[a] Reagents: (a) $(CH_3)_3SiCCH$, $(PPh_3)_2PdCl_2$, Et_3N, CuI, CH_3CN, room temperature, 1 h; (b) *n*-$Bu_4N^+F^-$, CH_3CN, room temperature, 1 h; (c) **40**, $(PPh_3)_2PdCl_2$, Et_3N, CuI, CH_3CN, room temperature, 1 h; (d) 1 M LiOH, room temperature, 1.5 h, 5% citric acid; (e) H_2, 5% Pd/C, 40 psi, room temperature, 3.5 h; (f) DCC/HOBt, DMF, CH_2Cl_2, **25**, room temperature, 48 h; (g) TFA, room temperature, 48 h; (g) TFA, room temperature, 3 h.

Lys dipeptide **25**, followed by removal of the remaining protecting groups with trifluoroacetic acid gave **48**, after HPLC purification.

Structure−Activity Relationships with *C. albicans* NMT. Tripeptide N-Terminal Chain Length Variations. In **3a**, it was surprising that an 11-aminoundecanoyl moiety could serve as a spatial replacement for the first four amino acid residues in

Table 1. Potencies of Peptidomimetic NMT Inhibitors[a]

compd	*C. albicans* NMT IC_{50} (μM)	compd	*C. albicans* NMT IC_{50} (μM)
3a	1.2 ± 0.14	**17a′**	365 ± 20
3b	16 ± 1.8	**17a**	0.78 ± 0.11
3c	16 ± 2.1	**17b**	>10
3d	19 ± 2.8	**17c**	1.2 ± 0.21
3e	3.9 ± 0.1	**17d**	5
3f	8.2 ± 0.34	**17e**	0.11 ± 0.03
3g	0.36 ± 0.06	**17f**	1.3 ± 0.07
3h	0.76 ± 0.08	**17g**	0.3 ± 0.03
4a	0.6 ± 0.03	**26a**	0.19 ± 0.02
4b	0.3 ± 0.01	**26b**	0.11 ± 0.04
4c	5.2 ± 0.64	**26c**	0.75 ± 0.01
4d	>100	**36**	0.52 ± 0.12
4e	0.27 ± 0.01	**37**	0.17 ± 0.01
8a	0.35 ± 0.01	**38**	0.34 ± 0.06
8b	0.69 ± 0.06	**43**	>10
16	6.7 ± 0.52	**44**	0.75 ± 0.22
3a′	>1000	**48**	0.043 ± 0.006

[a] Potency against the indicated NMT as assessed by IC_{50} using the peptide GNAASARR-NH_2 at its apparent K_m and myristoyl-CoA at 1 μM.[8c,21]

ALYASKLS-NH_2 and still yield an inhibitor with significantly greater potency (function).[11] To determine if the undecanoyl chain represented the optimal spacing between the N-terminal amino group and the critical Ser-Lys-Leu recognition elements, a systematic chain length scan was completed. The aminoundecanoyl **4a**, aminodecanoyl **4b**, aminononanoyl **4c**, aminoheptanoyl **4d**, and aminododecanoyl **4e** analogs were evaluated as inhibitors of *C. albicans* NMT. The data in Table 1 indicate that the activity of compounds **4a**, **4b**, and **4e** are comparable. Shorter chain lengths were not pursued since almost all inhibitory activity was lost with **4d**.

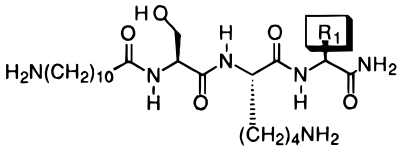
These surprising results indicate that one carbon atom can be added to or subtracted from the linking group connecting the N-terminal amine with the critical Ser-Lys-Leu moiety. The resulting inhibitors **4a**,**b**,**e** still exhibit greater potency than the starting octapeptide inhibitor **2**. This finding suggests that the flexibility of this 11-aminoundecanoyl chain in **4a** may permit a more optimal conformation of the inhibitor to be accessed than can exist in the octapeptide. The lack of limiting contacts with the residues in the enzyme's peptide binding pocket in **4a** may permit critical elements of recognition in the ligand to be presented to the host.

***N*-Alkyl Terminal Amine Substituents.** Analogs of ALYASKLS-NH_2, containing a β-alanine residue in place of alanine-1, were poor enzyme inhibitors (IC_{50} = 110 μM for *C. albicans* NMT).[11] Analogs containing a sarcosine residue in place of alanine-1, also displayed poor potency ($IC_{50} = 80 \pm 8$ μM for *C. albicans* NMT).[11] In analogs of **3a**, deletion of the primary amine in the 11-aminoundecanoyl moiety (*N*-undecanoyl-Ser-Lys-Leu-Ser-NH_2) reduces inhibitory potency by nearly 25-fold.[11] One would therefore expect that the N-terminal primary amino group in **3a** might be highly sensitive to *N*-alkyl substitution. As shown in Table 1, **8a** is about 2-fold more potent an inhibitor than **4a**, while the activity of **8b** is identical to that of **4a**. Thus, this inhibitor series demonstrates that NMT is capable of accommodating simple *N*-alkyl substituents at the N-terminus. These substituents presumably increase the basicity at this center. By imposing an extra atom at the N-terminus, these N-substituted inhibitors change the distance relationship(s) between the critical N-terminal amino group and the Ser-Lys-Leu moiety. Our findings therefore provide further evidence that recognition of these 11-aminoundecanoyl-containing inhibitors is more promiscuous than that of the parental inhibitor, ALYASKLS-NH_2.

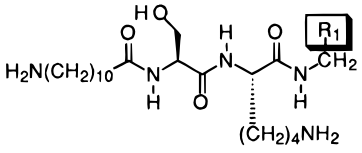
C-Terminus Variations. Analysis at the C-terminus of **3a** focused on understanding the metabolic stability at this center and whether the leucine side chain was optimal for potency. Tripeptide **3a** (amide) displayed little, if any, significant antifungal activity up to concentrations of 100 μM. When radiolabeled **3a** was incubated with crude extracts of *C. albicans*, one major metabolite **16** (carboxylic acid) was identified by HPLC. Since the inhibitory activity of **16** was about 10-fold lower than **3a** (Table 1), degradation of **3a** by either cellular carboxy peptidases or other types of proteases could explain its poor biological activity.

Lysinamides. One approach to improve stability entailed the removal of the carboxamide moiety. The isoamyl lysinamide dipeptide **17a** (corresponding to tripeptide **3a**) exhibited slightly greater inhibitory activity against the purified fungal enzyme (Table 1) than **3a**. While removal of the carboxamide moiety did not significantly reduce inhibitory potency in vitro, it did not improve antifungal activity. The specificity of compounds **3a** and **17a** for the NMT peptide binding site was highly dependent upon maintaining the L-configuration at the serine, lysine and leucine centers. This was confirmed by synthesizing the corresponding optical isomers **3a′** and **17a′**, which incorporated D-amino acids at the appropriate positions. Compound **3a′** contained D-amino acids at all three positions and exhibited an IC_{50} of 365 ± 20 μM against *C. albicans* NMT. Similarly, the D,D-Ser-Lys isomer **17a′** was significantly less active than its L,L-isomer **17a**, exhibiting an IC_{50} of >1 mM against *C. albicans* NMT.

To establish whether the leucine side chain was optimal, a series of dipeptide lysinamides were compared to their tripeptide counterparts containing various R_1 substituents. A direct comparison of the activities



3a-g



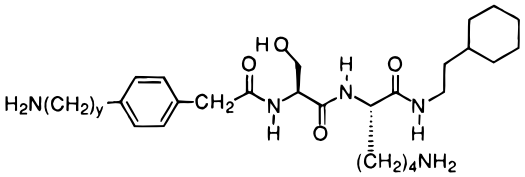
17a-g

(Table 1) of the tripeptide series **3a**−**g** with the dipeptide lysinamides **17a**−**d** gave a good correlation for the steric requirements at this R_1 position. Incorporating smaller substituents such as R_1 = H (**3b**) or CH_3 (**3c**) produced considerably weaker tripeptide inhibitors. Similarly, changing the isobutyl group to an isopropyl (**3d**, **17b**), *sec*-butyl (**3e**) or *tert*-butyl group (**17c**) reduced activity. Aromatic side chains (**3f**, **17d**) also reduced potency. There appeared to be a clear preference for lipophilic, aliphatic substituents at R_1 that maintained the proper distance from the lysine nitrogen amide center.

These results led to the incorporation of the cyclohexylalanine moiety in **3g** which significantly enhanced potency of this tripeptide. The corresponding cyclohexylglycine derivative **3h** was slightly less active. The *N*-(cyclohexylethyl)lysinamide dipeptide **17e** also exhibited enhanced potency relative to **17a**. Longer chain extensions (**17f**) or larger rings (**17g**) did not improve this activity. Kinetic studies indicated that **17e** was a competitive inhibitor versus the peptide substrate GNAASARR-NH_2 ($K_{i(app)}$ = 0.07 ± 0.01 μM).[21]

Compounds **17a** and **17e** were considerably more stable than **3a** upon incubation with crude extracts of *C. albicans*. No production of **16** was observed by HPLC after 24 h incubations with either **17a** or **17e**. One can conclude from these results that an isoamyllysinamide **17a** exhibits potency essentially identical to either the tripeptide SKL methyl ester **4a** or tripeptide SKL amide **3a**. Significantly better potency is observed with the *N*-(cyclohexylethyl)lysinamide analog **17e**.

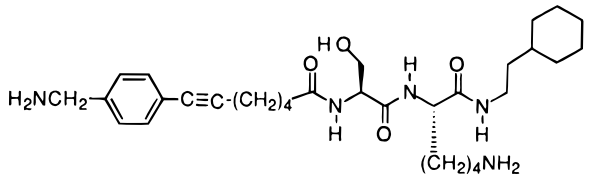
Conformationally Constrained Undecanoyl Chains. With this optimization of the C-terminus completed, our efforts focused on increasing the inhibitory potency of **17e** (IC_{50} = 0.11 ± 0.03 μM) by introducing conformational constraints into its flexible 11-aminoundecanoyl chain. Phenylene was selected as the rigidifying element and inserted at specific sites within the 11-aminoundecanoyl group of **17e**. Since the distance between the ω-amino moiety and the undecanoyl carbonyl group appeared to be important for recognition, we prepared analogs that maintained this spacing. Compounds **26a**−**c** contained phenylene insertions near the undecanoyl carbonyl group. The *p*-(ω-aminoalkyl)-phenacetyl ring was accommodated. The greatest inhibitory activity was observed with the *p*-aminohexyl substituent in **26b**, which retained all of the potency originally observed in **17e**. Shortening or lengthening this *p*-aminohexyl chain reduced activity. Kinetic studies established that **26b** was a competitive inhibitor versus the peptide substrate GNAASARR-NH_2 ($K_{i(app)}$ = 0.06 ± 0.004 μM).[21] Similarly, a direct comparison of the *meta*-substituted isomer **36** versus **26a** (Table 1) indicated that the *para*-substitution pattern was preferred.



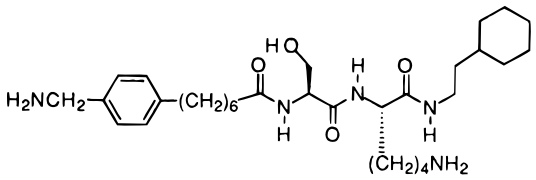
26a y = 5, IC_{50} = 0.19 ± 0.02 μM
26b y = 6, IC_{50} = 0.11 ± 0.04 μM
26c y = 8, IC_{50} = 0.75 ± 0.01 μM

A complementary series was also evaluated which inserted the phenyl ring closer to the N-terminus of the undecanoyl chain. The results indicated that a *p*-(ω-aminomethyl)phenyl ring could be tolerated at the N-terminal position. The added unsaturation site in the acetylene **37** gave slightly enhanced potency over the saturated analog **38**, but displayed no advantage over **17e**.

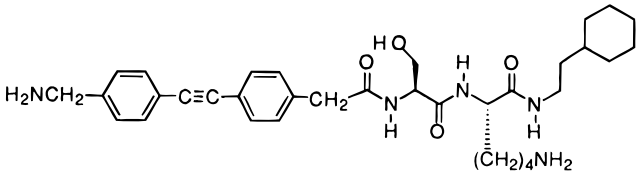
Since the combination of two rigidifying elements appeared to enhance potency, we sought to introduce three rigidifying elements with the diphenylacetylene analog **43**. Molecular-modeling studies suggested that the critical 13−14 Å distance between the N-terminal amino group and the carbonyl center of the undecanoyl chain in a fully extended, staggered conformation could be maintained with the side chain in **43**. The inhibitory potency of compound **43** was substantially reduced relative to either **26b** or **38**. Thus, while one or two rigidifying elements can be introduced into either end of the 11-aminoundecanoyl side chain of **17e**, the combination of three such elements eliminated most of this activity. The reduced derivative **44** regained much of the activity that was lost in **43**. This suggests that some conformational flexibility must be maintained near the center of this chain in order to accommodate a likely bend in the bound inhibitor conformation at this position. However, the combination of two phenyl rings as in **44** still gave reduced potency relative to either **26b** or **38**.



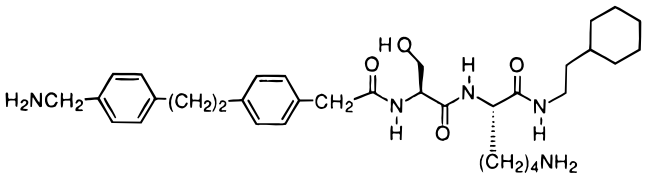
37 IC_{50} = 0.17 ± 0.01 μM



38 IC_{50} = 0.34 ± 0.06 μM



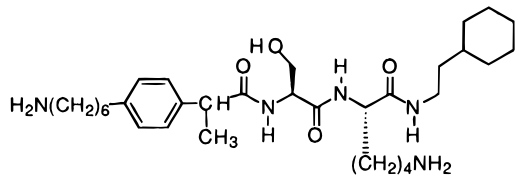
43 IC_{50} > 10 μM



44 IC_{50} = 0.75 ± 0.22 μM

Since the insertion of one phenyl ring near the carbonyl group in **26b** exhibited slightly better potency than the phenyl insertion near the N-terminus in **38**, we explored other derivatives of **26b**. The rationale for the synthesis of **48** evolved from the observation that substitution of glycine for alanine-4 in **1** (GLYGSKLS-NH_2) results in a 10-fold decrease in $K_{m(app)}$.[11] This finding indicated that the side chain methyl group of alanine-4 was an important recognition element that might enhance inhibitor binding affinity and suggested that analogs of **26b** with an α-methyl substituent, such as the phenylpropionamide **48**, might exhibit greater potency.

With an IC_{50} below 50 nM, **48** represents one of the most potent peptidomimetic inhibitors of NMT identified



48 $IC_{50} = 0.043 \pm 0.006\ \mu M$

to date. The submicromolar potency displayed by compounds **26b**, **38**, and **48** demonstrates that a reasonable variety of potent peptidomimetic inhibitors of *C. albicans* NMT can be prepared. Their potency may be attributable in part to the highly basic amine functionality present at the N-terminus. In the typical substrate GLYASKLS-NH_2, the glycine amine has a pK_a of about 8.0. As GLYASKLS-NH_2 is recognized by NMT, the enzyme most likely assists the removal of hydrogen from the glycylamine center during catalysis in order to produce the *N*-myristoylated adduct. The primary amines in **26b**, **38**, and **48** are much more basic (p$K_a \sim 10$) and are most likely bound as protonated amines, which may produce a potency advantage in this system.

Structure−Activity Relationships with Human NMT. All of the highly potent inhibitors of *C. albicans* NMT identified in this study were general inhibitors of NMT, as summarized in Table 2. Inhibitors **17a**,**e**,**g**, **26a**−**c**, and **36**−**38** all exhibited submicromolar potencies versus *C. albicans* NMT that were essentially maintained against human NMT. Human NMT recognizes a variety of peptide substrates that are different from those utilized by *C. albicans* NMT. These inhibitors thus reveal common elements of recognition at the peptide binding site between orthologous NMTs. As such, they may prove useful for exploring the functional significance of protein *N*-myristoylation in diverse eukaryotic systems.

A modest selectivity was observed for **48**. A higher selectivity, clearly out of the noise level, was only observed with **26c** and the more constrained inhibitor **44**, both of which exhibited much lower potency versus *C. albicans* NMT. This result suggests that one approach to enhance selectivity may involve identifying additional modifications that provide alternative means for constraining the conformation of these inhibitors and the presentation of the critical amine center relative to the Ser-Lys dipeptide.

Conclusions

We have prepared several new ω-aminoalkyl-substituted Ser-Lys dipeptide amides as potent, general inhibitors of NMT with reduced molecular weight and fewer chiral centers, starting from the weak octapeptide inhibitor ALYASKLS-NH_2 **2**. Remarkably, the first four amino acid residues (ALYA) in **2** can be replaced with the much simpler, flexible ω-aminoundecanoyl group or the partially constrained *p*-aminohexylphenacetyl moiety. Replacing the two C-terminal residues (LS) in **2** with a simple *N*-(cyclohexylethyl)amide enhances both inhibitory potency and metabolic stability. A fourth recognition element (alanine-4) was also identified that contributes to the high potency observed for **48**. None of the potent NMT inhibitors reported in this study exhibited significant antifungal activity against *C. albicans* ($EC_{50} \geq 100\ \mu M$). Our working hypothesis attributes this response to the presence of the two highly basic amino groups (p$K_a > 10$), which will likely be protonated under physiological conditions. Such highly charged species would not be expected to easily penetrate the lipophilic outer membrane of *C. albicans*. These results have led to successful synthetic efforts to identify suitable amine replacements for both the *p*-aminohexylphenacetyl substituent[8c,22] and the lysyl ϵ-amine moiety.[23]

Table 2. Potencies and Selectivities of Peptidomimetic NMT Inhibitors[a]

compd	*C. albicans* NMT IC_{50}, μM	human NMT IC_{50}, μM	selectivity[b]
17a	0.78 ± 0.11	0.42 ± 0.06	0.5
17e	0.11 ± 0.03	0.5 ± 0.37	4.5
17g	0.30 ± 0.03	1.14 ± 0.6	3.8
26a	0.19 ± 0.02	0.99 ± 0.16	5.2
26b	0.11 ± 0.04	0.8	7.3
26c	0.75 ± 0.01	53 ± 4	70
36	0.52 ± 0.12	1.8 ± 1	3.5
37	0.17 ± 0.01	0.76 ± 0.4	4.5
38	0.34 ± 0.06	1.5 ± 0.42	4.4
44	0.75 ± 0.22	62 ± 3	83
48	0.043 ± 0.006	0.79 ± 0.09	18

[a] Potency against the indicated NMT as assessed by IC_{50} using the peptide GNAASARR-NH_2 at its apparent K_m and myristoyl-CoA at 1 μM.[8c,21] [b] Selectivity is the ratio of the IC_{50} against human NMT to the IC_{50} against *C. albicans* NMT.

Experimental Section

Chemistry. General Comments. Unless otherwise stated, starting materials were obtained from commercial suppliers and were used without further purification. L-Amino acid derivatives were purchased from either Sigma, Applied Biosystems, Inc., or Bachem California. Solid-phase resins were obtained from Omni Biochem or Applied Biosystems, Inc. Unless otherwise stated, L-amino acids or their *N*-protected intermediates were used in all syntheses. All reactions were performed under anhydrous conditions in an atmosphere of argon. Melting points were determined using a Melt-Temp apparatus and are uncorrected.

Nuclear magnetic resonance proton spectra were recorded on a Varian XL-300 spectrometer, and chemical shifts (δ) are reported in ppm relative to tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Low-resolution mass spectra were recorded on a VG40-250T instrument, and high-resolution mass spectra were recorded on a Finnigan MAT 90 mass spectrometer operating in the FAB mode. Amino acid analyses were performed following hydrolysis in 6 N HCl at 150 °C in vacuo for 1.5 h using a Beckman 6300 high-performance analyzer.

Analytical reverse-phase high-performance liquid chromatography (HPLC) was carried out using a Waters Delta-Pak cartridge (C-18, 8 × 100 mm), eluting with 0.05% trifluoroacetic acid (TFA) in water (A) and 0.05% TFA in acetonitrile (B). The elution was carried out with a linear gradient from 5 to 70% of B in 30 min. The flow rate was adjusted to 1.0 mL/min, and the separation was monitored by UV absorbance at 215 nm. Preparative reverse-phase high-performance liquid chromatography was performed on a Waters Delta-Pak cartridge (C-18, 40 × 100 mm, 15 μm) using a linear gradient from 5 to 70% of B in 30 min. The flow rate was adjusted to 70 mL/min, and the separation was monitored by UV absorbance at 215 nm. All compounds isolated by preparative chromatography were reanalyzed by analytical HPLC and found to be >95% pure.

General Procedure for the Solid-Phase Synthesis of Tripeptides 3a−h, as Represented for the Preparation of 11-Aminoundecanoyl-Ser-Lys-Leu-NH_2 (3a). These peptides were assembled using an Applied Biosystems, Inc. (Model 430A) automated synthesizer employing standard *N*-BOC-amino acid coupling protocols on a *p*-methylbenzhydrylamine resin.[15] The preformed symmetrical anhydrides of the protected amino acids were made by combining the

appropriate *N*-BOC-amino acid (2 mmol) with dicyclohexylcarbodiimide (DCC, 1 mmol) in 10 mL of CH_2Cl_2 for 5 min, filtering to remove the urea byproduct, and then removing approximately half of the solvent by evaporation. After dilution with 5 mL of DMF, the solution was combined with the appropriate resin containing the growing peptide chain. After nitrogen mixing for 25 min, the peptide-resin was washed with CH_2Cl_2. The *N*-BOC group was removed with 60% trifluoroacetic acid (TFA) in CH_2Cl_2 for 15 min, and the resin was washed sequentially with CH_2Cl_2, 10% diisopropylethylamine (DIEA) in CH_2Cl_2, and CH_2Cl_2. Using this general protocol, the title compound was prepared from 4-methylbenzhydrylamine[15] resin (0.5 mmol, 0.7 mequiv/g), and the following amino acids were added sequentially to the growing peptide chain: *N*-BOC-leucine, *N*-α-BOC-lysine-(*N*-ϵ-*p*-Cl-Z), *N*,*N*-BOC-11-aminoundecanoic acid[13] was then activated and coupled using the standard automated protocol. The peptide-resin was treated with 10 mL of 90% HF/10% anisole for 60 min at 0 °C to remove the benzyl protecting groups and separate the peptide from the resin. After extraction of the peptide with 30% aqueous acetic acid, the compound was lyophilized and purified by reverse-phase HPLC using a linear gradient from 5% to 35% CH_3CN (with 0.05% TFA) in water (with 0.05% TFA) at 1.5%/min. The appropriate fractions containing product were combined and lyophilized. HPLC (>95%) purity was determined using a linear gradient of 1% to 35% CH_3CN (0.05% TFA) in water (0.05% TFA) at 1.75%/min: HPLC t_R = 15.07 min; ^{1}H NMR (CD_3OD) δ 6−2.18 (t, 2H), 2.70−2.75 (q, 4H), 3.56−3.61 (m, 2H), 4.16−4.28 (m, 3H), 7.04−7.10 (d, 1H), 7.73−7.80 (d, 1H), 7.98−8.03 (d, 1H), 8.15−8.20 (d, 1H); MW $C_{26}H_{53}N_6O_5$ calcd 529.4077 (M + H), found 529.4082 (M + H, HRFABMS). Amino acid analysis: Ser 1.03 (1.00); Lys 0.98 (1.00); Leu 1.02 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Gly-NH$_2$ (3b). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Gly was used in place of *N*-BOC-Leu: HPLC t_R = 12.89 min; MW $C_{22}H_{45}N_6O_5$ calcd 473.3451 (M + H), found 473.3451 (M + H, HRFABMS). Amino acid analysis: Ser 1.00 (1.00); Lys 1.00 (1.00); Gly 0.90 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Ala-NH$_2$ (3c). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Ala was used in place of *N*-BOC-Leu: HPLC t_R = 11.77 min; MW $C_{23}H_{47}N_6O_5$ calcd 487.3608 (M + H), found 487.3600 (M + H, HRFABMS). Amino acid analysis: Ser 0.88 (1.00); Lys 0.97 (1.00); Ala 1.03 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Val-NH$_2$ (3d). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Val was used in place of *N*-BOC-Leu: HPLC t_R = 14.04 min; ^{1}H NMR (DMSO-d_6) δ 0.78−0.83 (t, 6H), 1.25 (s, 14H), 1.48 1.54 (m, 6H), 1.65−1.74 (m, 1H), 1.87−1.97 (m, 1H), 2.05−2.12 (t, 2H), 2.71−2.76 (m, 4H), 3.44−3.53 (m, 2H), 4.15−4.30 (m, 3H), 7.08 (s, 1H), 7.32 (s, 1H), 7.88−7.90 (d, 1H), 8.09−8.12 (d, 1H); MW $C_{25}H_{51}N_6O_5$ calcd 514.3842 (M + H), found 514.3835 (M + H, HRFABMS). Amino acid analysis: Ser 1.01 (1.00); Lys 1.00 (1.00); Val 0.99 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Ile-NH$_2$ (3e). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Ile was used in place of *N*-BOC-Leu: HPLC t_R = 14.27 min; ^{1}H NMR (DMSO-d_6) δ 0.77−0.81 (t, 6H), 1.23 (s, 14H), 1.45 1.52 (m, 9H), 1.62−1.71 (m, 1H), 2.07−2.13 (t, 2H), 2.72−2.76 (m, 4H), 3.49−3.56 (m, 2H), 4.06−4.31 (m, 3H), 7.18 (s, 1H), 7.32 (s, 1H), 7.88−7.91 (d, 1H), 8.08−8.12 (d, 1H); MW $C_{26}H_{53}N_6O_5$ calcd 529.4077 (M + H), found 529.4076 (M + H, HRFABMS). Amino acid analysis: Ser 0.99 (1.00); Lys 1.00 (1.00); Ile 0.98 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Phe-NH$_2$ (3f). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Phe was used in place of *N*-BOC-Leu: HPLC t_R = 15.73 min; ^{1}H NMR (DMSO-d_6) δ 1.23 (s, 14H), 1.42−1.49 (m, 8H), 2.09−2.15 (t, 2H), 2.71−2.76 (m, 5H), 3.01−3.19 (dd, 1H), 3.45−3.61 (m, 2H), 4.02−4.13 (m, 1H), 4.28−4.38 (m, 2H), 7.10−7.25 (m, 7H), 7.79−7.84 (d, 1H), 7.90−7.94 (d, 1H), 8.16 8.20 (d, 1H); MW $C_{29}H_{51}N_6O_5$ calcd 563.3921 (M + H), found 563.3953 (M + H, HRFABMS). Amino acid analysis: Ser 0.96 (1.00); Lys 0.96 (1.00); Phe 1.04 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-cyclohexylAla-NH$_2$ (3g). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-cyclohexyl-Ala was used in place of *N*-BOC-Leu: HPLC t_R = 18.14 min; MW $C_{29}H_{57}N_6O_5$ calcd 569.4390 (M + H), found 569.4399 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-cyclohexylGly-NH$_2$ (3h). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-cyclohexyl-Gly was used in place of *N*-BOC-Leu. *N*-BOC-cyclohexylGly was prepared from cyclohexyl-Gly and di-*tert*-butyl dicarbonate using the procedure of Tarbell et al.:[19] HPLC t_R = 16.42 min; ^{1}H NMR (DMSO-d_6) δ 0.89−1.11 (m, 4H), 1.24 (s, 13H), 1.42−1.71 (m, 12H), 2.06−2.11 (t, 2H), 2.68-2.77 (m, 4H), 3.50−3.53 (d, 2H), 4.02−4.30 (m, 3H), 7.15 (s, 1H), 7.33 (s, 1H), 7.84−7.91 (d, 1H), 8.03−8.13 (d, 1H); MW $C_{28}H_{55}N_6O_5$ calcd 555.4234 (M + H), found 555.4242 (M + H, HRFABMS). Amino acid analysis: Ser 0.96 (1.00); Lys 1.04 (1.00).

(11-Aminoundecanoyl)-D-Ser-D-Lys-Leu-NH$_2$ (3a′). The title compound was prepared using the same procedure as described for **3a**, except *N*-BOC-D-Lys(Z-*p*-Cl) and *N*-BOC-D-Ser(O-Bn) were substituted for their respective L-amino acid counterparts: HPLC t_R = 15.20 min; ^{1}H NMR (DMSO-d_6) δ 0.77−0.88 (dd, 6H), 1.23 (s, 15H), 1.42−1.55 (m, 10H), 1.70−1.81 (m, 1H), 2.10-2.18 (t, 2H), 2.68−2.80 (m, 4H), 3.52−3.63 (m, 2H), 4.10 4.27 (m, 3H), 6.96 (s, 1H), 7.23 (s, 1H), 7.81−7.85 (d, 1H), 7.95−7.99 (d, 1H), 8.03−8.13 (d, 1H); MW $C_{26}H_{53}N_6O_5$ calcd 529.4077 (M + H), found 529.4066 (M + H, HRFABMS). Amino acid analysis: Ser 0.98 (1.00); Lys 1.01 (1.00); Leu 1.01 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-Leu-OH (16). This compound was prepared using the same procedure as described for **3a**, except *N*-BOC-Leu-OCH_3-Pam-resin (0.5 mmol) was used in place of the 4-methylbenzhydrylamine resin and *N*-BOC-Leu: HPLC t_R = 15.27 min; ^{1}H NMR (DMSO-d_6) δ 0.79−0.86 (dd, 6H), 1.23 (s, 14H), 1.42−1.56 (m, 10H), 1.65−1.75 (m, 1H), 2.06-2.17 (m, 2H), 2.70−2.78 (m, 4H), 3.43−3.56 (m, 2H), 4.09 4.31 (m, 3H), 7.85−8.00 (m, 5H); MW $C_{26}H_{52}N_5O_6$ calcd 530.3918 (M + H), found 530.3919 (M + H, HRFABMS). Amino acid analysis: Ser 1.02 (1.00); Lys 1.00 (1.00); Leu 1.03 (1.00).

Lys(Z)-Leu-OMe, Hydrochloride (6). A mixture of *N*-BOC-Lys(Z)-OSu (*N*-hydroxysuccinimide) ester (**5**, 5.0 g, 10.47 mmol) and leucine methyl ester hydrochloride (1.902 g, 10.47 mmol) in dry dichloromethane (25 mL) was stirred at 0 °C, and triethylamine (1.36 mL, 10.47 mmol) was added. After being stirred for 16 h at room temperature, the reaction mixture was diluted with dichloromethane (200 mL), and the reaction mixture was washed with dilute hydrochloric acid (1 N, 100 mL), saturated sodium bicarbonate (100 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated to afford 4.70 g (88%) of the desired protected dipeptide. Dioxane/HCl (4 N, 20 mL) was added to this dipeptide at 0 °C, and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated to dryness, and excess HCl was chased by evaporating with toluene. The desired product **6** was obtained as a colorless solid: 4.0 g (97%); ^{1}H NMR (CD_3OD) δ 0.93, 0.96 (dd, 6H, J = 6.4 Hz), 1.46−1.92 (m, 6H), 3.16 (t. 2H, J = 7 Hz), 3.67 (s, 3H), 3.92 (t, 1H, J = 6.3 Hz), 4.49 (t, 1H, J = 7.3 Hz), 5.06 (s, 2H), 7.29−7.34 (m, 5H); MW $C_{21}H_{33}N_3O_5$ calcd 408.2498 (M + H), found 408.2483 (M + H, HRFABMS).

Ser(OBn)-Lys(Z)-Leu-OMe, Hydrochloride (7). A mixture of *N*-BOC-Ser(OBn)-OSu (3.629 g, 9.25 mmol) and **6** (4.10 g, 9.25 mmol) in dry dichloromethane (30 mL) was stirred at 0 °C, and triethylamine (1.28 mL, 9.25 mmol) was added. After being stirred for 16 h at room temperature, the reaction mixture was diluted with dichloromethane (200 mL). The resulting mixture was washed with dilute hydrochloric acid (1 N, 100 mL), saturated sodium bicarbonate (100 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated to afford 5.70 g (90%) of *N*-BOC-Ser(OBn)-Lys(Z)-Leu-OMe. Dioxane/HCl (4N, 20 mL) was added to this product (5.7 g, 8.323 mmol) at 0 °C, and the solution was stirred for 4 h at room temperature. The reaction mixture was concentrated to dryness, and the excess HCl was chased by evaporating with toluene. The desired product **7** was obtained as a colorless solid: 5.0 g (97%); ^{1}H NMR (CD_3OD) δ 0.85 (d, 3H, J = 6.3 Hz), 0.90 (d, 3H, J = 6.3 Hz), 1.43−1.82 (m, 11H), 3.12 (t, 2H,

J = 6.7 Hz), 3.66 (s, 3H), 3.68−3.93 (m, 2H), 4.42 (m, 2H), 4.60 (s, 2H), 5.05 (s, 2H), 7.32−7.37 (m, 10H); MW $C_{31}H_{44}N_4O_7$ calcd 585.3288 (M + H), found 585.3279 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (4a). Coupling of *N*-BOC-11-aminoundecanoic acid[13] and **7** using the above procedure afforded 0.85 g (30%) of the desired (11-aminoundecanoyl)-Ser(OBn)Lys(Z)Leu-OMe as a pale yellow solid. The (*N*-BOC-11-aminoundecanoyl)-Ser-(OBn)-Lys(Z)-Leu-OMe (0.4 g, 0.46 mmol) was treated with 4 N HCl in dioxane (10 mL). The reaction mixture was stirred for 1.5 h at room temperature. The reaction mixture was concentrated and dried in vacuo to yield a residue which was hydrogenolyzed to yield 0.1 g (88%) of the desired product **4a** as a white solid: ^{1}H NMR (CD_3OD) δ 0.93 (dd, 6H, J = 6.23 Hz), 1.21−1.94 (m, 25H), 2.28 (t, 2H, J = 7.55 Hz), 2.85-2.93 (m, 4H), 3.59−3.86 (m, 6H), 4.42 (dd, 2H, J = 4.9 Hz); MW $C_{27}H_{53}N_5O_6$ calcd 544.4074 (M + H), found 544.4068 (M + H, HRFABMS).

(10-Aminodecanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (4b). Using the procedure described above for **4a** but substituting 10-azidodecanoic acid,[14] the desired product **4b** was obtained: ^{1}H NMR (CD_3OD) δ 0.89 and 0.94 (2d's, 6H, J = 6.3 Hz), 1.12−1.95 (m, 23H), 2.28 (t, 2H, J = 7.3 Hz), 2.86 (t. 4H, J = 7.4 Hz), 3.69 (s, 3H), 3.78 (dq, 2H, J = 10.8, 5.7 Hz), 4.42 (m, 4H); MW $C_{26}H_{51}N_5O_6$ calcd 530.3918 (M + H), found 530.3972 (M + H, HRFABMS).

(9-Aminononanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (4c). Using the procedure described above for **4a** but substituting 9-azidononanoic acid[14] in the coupling with **7**, 1.40 g (71%) of the desired pure azido ester was obtained. A solution of (9-azidononanoyl)-Ser(OBn) Lys(Z)-Leu-OMe was hydrogenolyzed to afford 0.180 g (83%) of **4c**. ^{1}H NMR (CD_3OD) δ 0.89, 0.94 (2 d's, 6H), 1.12−1.95 (m, 21H), 2.29 (t, 2H, J = 7.9 Hz), 2.91 (m, 4H), 3.69 (s, 3H), 3.68−3.87 (m, 3H), 4.40 (m, 3H); MW $C_{25}H_{49}N_5O_6$ calcd 516.3761(M + H), found 516.3821 (M + H, HRFABMS).

(Aminoheptanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (4d). Using the reaction sequence described for **4a**, but using 7-azidoheptanoic acid[14] in place of *N*-BOC-11-aminoundecanoic acid, **4d** was prepared: ^{1}H NMR (CD_3OD) δ 0.89 and 0.94 (2 d's, 6H, J = 6 Hz), 1.38 (m, 1H), 1.92 (m, 17H), 2.30 (t, 2H, J = 7.7 Hz), 2.85 (t, 4H, J = 7.9 Hz), 3.69 (s, 3H), 3.66−3.86 (m, 3H), 4.42 (m, 3H); MW $C_{23}H_{45}N_5O_6$ calcd 488.3448 (M + H), found 488.3432 (M + H, HRFABMS).

(12-Aminododecanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (4e). Using the sequence above and replacing *N*-BOC-11-aminoundecanoic acid with 12-azidododecanoic acid,[14] the desired product **4e** was obtained: ^{1}H NMR (CD_3OD) δ 0.89 (d, 3H, J = 5.9 Hz), 0.94 (d, 3H, J = 5.9 Hz), 1.16−1.92 (m, 27H), 2.28 (m, 2H), 2.93 (m, 4H), 3.69−3.85 (m, 3H), 3.69 (s, 3H), 4.40 (m, 4H); MW $C_{28}H_{55}N_5O_6$ calcd 558.4231 (M + H), found 558.4275 (M + H, HRFABMS).

***N*-(Carbobenzyloxy)-*N*-methyl-11-aminoundecanoic Acid (10c).** A mixture of 11-bromoundecanoic acid (**9**, 6.0 g) and aqueous methylamine (40%, 40 mL) in methanol (20 mL) was stirred for 18 h at room temperature. The reaction mixture was concentrated. The residue obtained was dissolved in water, basified with sodium hydroxide, and concentrated again. The solid obtained was the desired secondary amine. This crude product (2.15 g) was dissolved in dioxane (30 mL), and NaOH (15 mL, 5 N) was added. To this solution was added *N*-carbobenzyloxy chloride (Z-Cl, 2 g), followed by sodium carbonate (2.06 g). After being stirred for 18 h, the reaction mixture was diluted with water (200 mL) and acidified with 2 N HCl. The reaction mixture was extracted with ether (3 × 100 mL), dried, and concentrated. Purification of the residue by flash column chromatography on silica gel eluting with ethyl acetate afforded 1.68 g of **10c**: ^{1}H NMR ($CDCl_3$) δ 1.23−1.68 (m, 16H), 2.36 (t, 2H, J = 7.4 Hz), 2.94 (s, 3H), 3.29 (t, 2H, J = 5.7 Hz), 5.15 (s, 2H), 7.30 4.55 (m, 5H); MW $C_{20}H_{31}NO_4$ calcd 350.2331 (M + H), found 350.2339 (M + H, HRFABMS).

***N,N*-Dimethyl-11-aminoundecanoic Acid (10b).** A mixture of 11-bromoundecanoic acid (4.02 g) and dimethylamine (100 mL) in methanol (10 mL) was stirred for 18 h at room temperature. The reaction mixture was concentrated. The residue obtained was dissolved in water, basified with sodium hydroxide, and concentrated again. The solid obtained was dissolved in methanol, acidified to pH 4, and concentrated again. The residue was triturated with ethyl alcohol and concentrated to afford 4.0 g of the desired product **10b**: ^{1}H NMR (CD_3OD) δ 1.33−1.75 (m, 16H), 2.27 (t, 2H, J = 7.4 Hz), 2.87 (s, 6H), 3.08−3.14 (m, 2H); MW $C_{13}H_{27}NO_2$ calcd 230.2120 (M + H), found 230.2130 (M + H, HRFABMS).

(*N*-(Carbobenzyloxy)-*N*-methyl-11-aminoundecanoyl)-Ser(OBn)-Lys(Z)-Leu-OMe (11a). Using the procedure described for the synthesis of **4a**, coupling of **7** and **10c** afforded 0.10 g (33%) of the desired pure **11a**: ^{1}H NMR ($CDCl_3$) δ 0.80 (q, 6H, J = 6.2 Hz), 0.95−1.81 (m, 25H), 2.13 (t, 2H, J = 6.5 Hz), 2.82 (s, 3H), 3.04 (t, 2H, J = 6.2 Hz), 3.17 (t, 2H, J = 7.2 Hz), 3.37 (m, 1H), 3.52−3.85 (m, 2H), 3.57 (s, 3H), 4.27−4.41 (m, 2H), 4.44 (s, 2H), 4.52 (t, 1H, J = 5.5 Hz), 5.02 (s, 2H), 7.15−7.30 (m, 15H), 7.53−7.62 (m, 2H); MW $C_{51}H_{73}N_5O_{10}$ calcd 916.5436 (M + H), found 916.5436 (M + H, HRFABMS).

(*N*-Methyl-11-aminoundecanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (8a). Hydrogenolysis of **11a,** using the procedure described for the synthesis of **4a**, afforded 0.04 g of **8a**: ^{1}H NMR (CD_3OD) δ 0.89 and 0.94 (2 d's, 6H, J = 6.1 Hz), 1.08−1.97 (m, 25H), 2.27 (t, 2H, J = 7.6 Hz), 2.69 (s, 3H), 2.92−3.0 (m, 4H), 3.45 (m, 1H), 3.69 (s, 3H), 3.69−3.85 (m, 2H), 4.3−4.78 (m, 2H), 8.20 (d, 1H, J = 7.6 Hz), 8.28 (d, 1H, J = 7.7 Hz); MW $C_{28}H_{55}N_5O_6$ calcd 558.4231 (M + H), found 558.4264 (M + H, HRFABMS).

(*N,N*-Dimethyl-11-aminoundecanoyl)-Ser-Lys-Leu-OMe, Hydrochloride (8b). This compound was prepared using the procedure described for the synthesis of **8a**: ^{1}H NMR (CD_3OD) δ 0.89 and 0.94 (2 d's, 6H, J = 7.9 Hz), 1.26−1.95 (m, 25H), 2.26 (t, 2H, J = 7.3 Hz), 2.86 (s, 6H), 2.93 (t, 2H, J = 7.2 Hz), 3.10 (m, 2H), 3.69 (s, 3H), 3.68−3.84 (m, 2H), 4.40 (m, 2H); MW $C_{29}H_{57}N_5O_6$ calcd 572.4387 (M + H), found 572.4432 (M + H, HRFABMS).

10-Azidodecanoic Acid. A mixture of 10-bromodecanoic acid (6.0 g, 23.89 mmol) and sodium azide (7.0 g, 107.7 mmol) was stirred in dimethyl sulfoxide (200 mL) for 24 h. The reaction mixture was diluted with water (300 mL) and extracted with ether (3 × 300 mL). The ether layer was dried and concentrated to afford 5.0 g (quantitative) of the desired product as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.27−1.67 (m, 14H), 2.37 (t, 2H, J = 7.5 Hz), 3.28 (t, 3H, J = 6.9 Hz); MW $C_{10}H_{19}N_3O_2$ calcd 214.1556 (M + H), found 214.1563 (M + H, HRFABMS).

12-Azidododecanoic Acid. This compound was prepared as a colorless liquid in a similar fashion from 12-bromododecanoic acid in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.19−1.67 (m, 18H), 2.35 (t, 2H, J = 7.6 Hz), 3.27 (t, 2H, J = 6.9 Hz); MW $C_{12}H_{23}N_3O_2$ calcd 242.1869 (M + H), found 242.1855 (M + H, HRFABMS).

***N*-Z-lysine Isoamylamide Hydrochloride (18a).** *N*-α-BOC-*N*-ϵ-Z-lysine *N*-hydroxysuccinimide ester (**5**, 1.00 g, 2.0 mmol) and isoamylamine (261.0 mg, 3.00 mmol) were mixed in dichloromethane (15 mL) at room temperature for 2 h. The solution was poured into diethyl ether (50.0 mL) and extracted with 10% aqueous hydrochloric acid (3 × 25 mL), 10% aqueous sodium hydroxide (3 × 25 mL), and saturated ammonium chloride (1 × 25 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure to afford *N*-α-BOC-*N*-ϵ-Z-lysine isoamylamide (899.0 mg, 1.97 mmol) as a semisolid (99% yield). The *N*-α-BOC-*N*-ϵ-Z-Lysine isoamylamide (1.95 g, 4.85 mmol) was mixed in dichloromethane. Anhydrous hydrogen chloride gas was bubbled through the solution for 15 min. The solution was stirred for 30 min at room temperature, and the solvent was removed at reduced pressure to afford **18a** (1.65 g, 4.80 mmol) as a foam (98% yield): ^{1}H NMR (CD_3OD) δ 0.90 (d, 6H, J = 6.7 Hz), 1.40−1.70 (m, 8H), 1.86−1.89 (m, 1H), 3.11−3.14 (m, 2H), 3.17−3.29 (m, 2H), 3.90−3.93 (m, 1H), 5.05 (s, 2H), 7.26−7.32 (m, 5H); MW $C_{19}H_{31}N_3O_3$ calcd 350.2444 (M + H), found 350.2453 (M + H, HRFABMS).

***O*-Benzyl-Ser-*N*-ϵ-Z-lysine Isoamylamide, Hydrochloride (19a).** A mixture of *N*-ϵ-Z-lysine isoamylamide hydrochloride (**18a**, 682 mg, 1.71 mmol), triethylamine (300 mg, 3.00 mmol), and *N*-BOC-*O*-benzyl-serine *N*-hydroxysuccinimide ester (744 mg, 1.90 mmol) in methylene chloride (25 mL) was stirred for 16 h. The solution was poured into diethyl ether

(30 mL) and extracted with 10% aqueous hydrochloric acid (3 × 40 mL), 10% aqueous sodium hydroxide (3 × 40 mL), and saturated ammonium chloride (2 × 40 mL). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure to afford **19a** as a semisolid (96% yield): ^{1}H NMR (CD_3OD) δ 0.86 (d, 6H, J = 6.8 Hz) 1.32−1.79 (m, 8H), 3.06−3.30 (m, 4H), 3.72 3.94 (m, 2H), 4.21 (m, 1H), 4.34 (m, 1H), 4.60 (s, 2H), 5.05 (s, 2H), 7.26−7.33 (m, 10H); MW $C_{29}H_{42}N_4O_5$ calcd 527.3233 (M + H), found 527.3244 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys Isoamylamide, Trifluoroacetate (17a). 11-Azidoundecanoic acid[14] (172 mg, 0.757 mmol) was dissolved in methylene chloride (5 mL) at room temperature. Carbonyldiimidazole (113 mg, 0.77 mmol) was added, and the solution was stirred for 15 min. *O*-Benzyl-Ser-*N*-ϵ-Z-Lys isoamylamide hydrochloride (**19a**, 200 mg, 0.34 mmol) and triethylamine (200 mg, 2.00 mmol) were added, and the solution was stirred at room temperature for 16 h. Methylene chloride (20 mL) was added, and the solution was extracted with 10% aqueous HCl (3 × 10 mL) followed by sodium bicarbonate (3 × 10 mL). The solution was dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. The resulting (11-azidoundecanoyl)-*O*-benzyl-L-Ser-*N*-Z-Lys isoamylamide (150 mg, 0.204 mmol) was isolated as a white foam (55% yield). This amide (40 mg, 0.054 mmol) was dissolved in methanol (5.0 mL) and trifluoroacetic acid (500 μL). 10% Palladium on carbon (20 mg) was added, and the mixture was stirred under hydrogen (55 psi) for 16 h at room temperature. The catalyst was removed by filtration, and the solvent was removed at reduced pressure to afford **17a** (40 mg, 0.045) as a waxy solid (81% yield): ^{1}H NMR (CD_3OD) δ 0.90 (d, 6H, J = 6.5 Hz), 1.28−1.98 (m, 25H), 2.25 (t, 2H, J = 7.2 Hz), 2.80−2.95 (m, 4H), 3.66−3.86 (m, 2H), 4.29−4.41 (m, 2H); MW $C_{25}H_{51}N_5O_4$ calcd 486.4019 (M + H), found 486.4021 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys Isobutylamide, Trifluoroacetate (17b). This compound was prepared by replacing isoamylamine in the above sequence (**5**−**18a**-**19a**−**17a**) with isobutylamine: ^{1}H NMR (CD_3OD) δ 0.88 (t, 6H, J = 6.8 Hz), 1.10−2.00 (m, 23H), 2.54 (t, 2H, J = 7.2 Hz), 2.90−2.92 (m, 2H), 2.98 (t, 2H, J = 6.5 Hz), 3.67−3.85 (m, 2H), 4.35 (m, 2H). FABMS m/z = 472 (M + H); MW $C_{24}H_{49}N_5O_4$ calcd 472.3683 (M + H), found 472.3847 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys Phenethylamide, Trifluoroacetate (17d). This compound was prepared by replacing isoamylamine in the above sequence (**5**−**18a**−**19a-17a**) with phenethylamine: yield 56%; ^{1}H NMR (CD_3OD) δ 1.21−1.81 (m, 22H), 2.26 (t, 2H, J = 8.4 Hz), 2.74−2.94 (m, 6H), 3.38−3.40 (m, 2H), 3.66−3.88 (m, 2H), 4.28−4.40 (m, 2H), 7.02−7.40 (m, 5H); MW $C_{28}H_{49}N_5O_4$ calcd 520.3863 (M + H), found 520.3860 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys-(3-cyclohexyl)propylamide, Hydrochloride (17f). This compound was prepared by replacing isoamylamine in the above sequence (**5**−**18a**−**19a**−**17a**) with 3-cyclohexylpropylamine: yield: 47%; ^{1}H NMR (CD_3OD) δ 0.86−2.0 (m, 39H), 2.29 (t, 2H, J = 7.4 Hz), 2.93 (m, 4H), 3.13 (t, 2H, J = 4.1 Hz), 3.71−3.76 (m, 2H), 4.35 (m, 2H); MW $C_{29}H_{57}N_5O_4$ calcd 540.4489 (M + H), found 540.4481 (M + H, HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys Cyclooctylethylamide, Hydrochloride (17g). The titled compound was prepared by replacing isoamylamine in the above sequence (**5**−**18a**−**19a**−**17a**) with cyclooctylethylamine (see below): yield 99%; ^{1}H NMR (CD_3OD) δ 4.31−4.38 (m, 2H), 3.65−3.88 (m, 2H), 3.18 (t, 2H, J = 5.8 Hz), 2.87−2.92 (m, 3H), 2.28 (t, 3H, 7.3 Hz), 1.32−1.74 (m, 40H); MW $C_{30}H_{59}N_5O_4$ calcd 554.4645, (M + H), found 554.4677 (M + H, HRFABMS).

(11-Aminoundecanoyl)-D-Ser-D-Lys Isoamylamide, Trifluoroacetate (17a′). The desired compound was prepared by substituting D-serine and D-lysine intermediates for their L-serine and L-lysine counterparts in the synthesis of **17a**: ^{1}H NMR (CD_3OD) δ 0.89 (d, 6H, J = 6.5 Hz), 1.28−1.44 (m, 25H), 2.25 (t, 2H, J = 7.2 Hz), 2.85 (t, 2H, J = 6.8 Hz), 3.66−3.86 (m, 2H), 4.29−4.41 (m, 2H); MW $C_{25}H_{51}N_5O_4$ calcd 486.4019 (M + H), found 486.4021 (M + H, HRFABMS).

Ser(OBn)-Lys(Z)-OMe, Hydrochloride (21). A mixture of EDC (8.0 g, 41,73 mmol), HOBt (5.63 g, 41.73 mmol), and Ser(*O*-benzyl)-OH (12.45 g, 41.73 mmol) was stirred in DMF (300 mL) at room temperature for 2 h. To this reaction mixture was added Lys(Z)-OMe·HCl (**20**, 13.80 g, 41.73 mmol), followed by triethylamine (5.81 mL), and stirring was continued for 18 h. The residue was dissolved in dichloromethane (1 L), and the reaction mixture was washed with dilute hydrochloric acid (1 N, 500 mL), saturated sodium bicarbonate (500 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated to afford 23 g (quantitative) of the *N*-BOC-protected dipeptide. This compound was added to 4 N HCl in dioxane (80 mL), and the mixture was stirred for 2 h. The solvent was removed in vacuo, and the excess HCl was removed by evaporating with toluene to afford 20.0 g (quantitative) of **21**: ^{1}H NMR (CD_3OD) δ 1.30−1.90 (m, 6H), 3.10 (m, 2H), 3.65 (s, 3H), 3.70−3.95 (m, 2H), 4.15 (m, 1H), 4.4 (m, 1H), 4.55 (s, 2H), 5.1 (s, 2H), 7.3−7.5 (m, 10H); MW $C_{25}H_{33}N_3O_6$ calcd 472.2448 (M + H), found 472.2480 (M + H), HRFABMS).

(11-Azidoundecanoyl)-Ser(OBn)-Lys(Z)-OH (22). A mixture of EDC (5.74 g, 29.93 mmol), HOBt (4.05 g, 29.93 mmol), and 11-azidoundecanoic acid[14] (6.80 g, 29.93 mmol) was stirred in DMF (350 mL) for 2 h at room temperature. The dipeptide **21** (15.21 g, 29.93 mmol) was added followed by triethylamine (4.16 mL), and then the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated, and the residue was dissolved in dichloromethane (1 L). This solution was washed with dilute hydrochloric acid (1 N, 300 mL), saturated sodium bicarbonate (300 mL), and brine. The organic layer was dried ($MgSO_4$) and concentrated to afford 20 g (quantitative) of the desired methyl ester. A solution of this methyl ester (5.0 g, 7.346 mmol) and lithium hydroxide (0.42 g, 17.50 mmol) in methanol (100 mL) and water (2 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with water (200 mL), acidified with dilute aqueous HCl, and extracted with ethyl acetate. The organic layer was dried and concentrated to afford 4.20 g of the desired acid **22** as a solid: ^{1}H NMR ($CDCl_3$) δ 1.26−1.89 (m, 24H), 2.25 (t, 2H, J = 7.3 Hz), 3.08 (q, 2H, J = 6.4 Hz), 3.24 (t, 2H, J = 6.4 Hz), 3.72 (m, 2H), 4.38−4.67 (m, 4H), 5.04 (s, 2H), 7.26−7.34 (m, 10H); MW: $C_{35}H_{50}N_6O_7$ calcd 667.3819 (M + H), found 667.3799 (M + H), HRFABMS).

(11-Aminoundecanoyl)-Ser-Lys-(3,3-dimethybutyl)-amide, Hydrochloride (17c). HOBt (0.041 g, 0.3 mmol), EDC (0.058 g, 0.3 mmol), and **22** (0.2 g, 0.3 mmol) were mixed and stirred in anhydrous DMF (5 mL) at 0−5 °C. 3,3-Dimethylbutylamine (0.03 g, 0.3 mmol) was dissolved in 0.5 mL of DMF and then was added to the above solution at 0−5 °C. The reaction mixture was stirred at 0−5 °C for 30 min and at room temperature for 18 h. The reaction was diluted with dichloromethane. The organic solution was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to give 0.155 g (70%) of the desired amide. This amide (0.27 g, 0.35 mmol) was dissolved in 15 mL of methanol, and 5% palladium on carbon (0.14 g) and 1 N HCl (0.37 mL) were added. The mixture was stirred under 45 psi of gaseous hydrogen for 72 h at room temperature. The catalyst was filtered through Celite and washed with excess methanol. The filtrate was concentrated and purified by reverse phase HPLC to give 0.08 g (31%) of **17c** as a clear gum. ^{1}H NMR (CD_3OD) δ 1.33−1.95 (m, 37H), 2.26 (t, 2H, J = 7.57 Hz), 2.88−2.95 (m, 4H), 3.67−3.73 (m, 1H), 3.82−3.98 (m, 1H), 4.30−4.36 (m, 2H); MW $C_{28}H_{55}N_5O_4$ calcd 526.4332 (M + H), found 526.4394 (M + H, HRFABMS).

Cyclooctylethylamine. (Cyanomethyl)cyclooct-1-ene (prepared according to literature procedures[20] starting from cyclooctanone, 5.0 g) was dissolved in THF (100 mL), and lithium aluminum hydride (2.0 g) was added in small quantities. The mixture was heated at reflux for 2 h. A 5% solution of sodium hydroxide was carefully added to the reaction mixture until a clear supernatant resulted. The reaction mixture was cooled, and the supernatant was filtered and concentrated to afford 4.8 g (92%) of the desired product as an oil: ^{1}H NMR ($CDCl_3$) δ 1.18−2.7 (m, 19H); MW $C_{10}H_{21}N$ calcd 156.1752 (M + H), found 156.1759 (M + H, HRFABMS).

Z-Lys(BOC)-2-cyclohexylethylamide (24). A mixture of Z-Lys(BOC)-*O*-*p*-nitrophenyl ester (**23**, 2.00 g, 4 mmol), hydroxybenzotriazole (HOBt, 0.53 g, 3.5 mmol), and 2-cyclohexylethylamine (1.24 g, 9.7 mmol) in dimethylacetamide (5.00 mL)

was stirred at room temperature for 48 h. After the removal of the solvent in vacuo, the residue was partitioned between EtOAc (50 mL) and cold 0.5 N NaOH (25 mL). The organic phase was successively washed with 0.5 N NaOH, 5% citric acid (3 × 20 mL), and water, dried (Na_2SO_4), and concentrated. The resulting residue was triturated with ether, cooled, and filtered, and the precipitate was washed thoroughly with ether and dried to give 1.6 g (82%) of **24** as a white powder. An analytical sample of **24** was obtained by crystallization from EtOAc: mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5H), 6.0 (br, 1H), 5.45 (br, 1H), 5.1 (s, 2H), 4.6 (br, 1H), 4. 18 (m, 1H), 3.25 (m, 2H), 3.1 (m, 2H), 1.85 (m, 1H), 1.7 (m, 6H), 1.6−1.4 (s over m, 19H), 0.9 (m, 2H); MW $C_{27}H_{43}N_3O_5$ calcd 490.3281 (M + H), found 490.3257 (M + H, HRFABMS).

Ser(O-*t*-Bu)Lys(BOC)-2-cyclohexylethylamide (25). A solution of **24** (1.3 g, 2.66 mmol) in methanol (25 mL) containing acetic acid (0.2 mL) and 5% Pd/C (0.3 g) was hydrogenolyzed at atmospheric pressure for 1 h. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was dried in a desiccator for 3 h and used in the following reaction without purification. To a solution of Z-Ser-(*O*-*t*-Bu)-OH (1.0 g, 3.4 mmol) and HOBt (0.55 g, 3.6 mmol) in dichloromethane (20 mL) and dimethylacetamide (3 mL) was added DCC (0.73 g, 3.5 mmol) dissolved in dichloromethane (10 mL), and the mixture was stirred at 0 °C for 1.5 h and filtered. The filtrate was added to a solution of the isolated amine acetate hydrogenolysis product in dimethylacetamide (2 mL) and *N*-methylmorpholine (0.4 mL). The resulting mixture was stirred at room temperature for 48 h and then was concentrated in vacuo. The residue was partitioned between cold 0.5 N NaOH (20 mL) and EtOAc (40 mL). The organic phase was washed successively with 0.5 N NaOH (20 mL), followed by water (2 × 20 mL), 5% citric acid (2 × 25 mL), and water, dried (Na_2SO_4), and concentrated under reduced pressure to afford a white powder. This material was triturated with ether and filtered, and the white precipitate was washed with ether and dried to give 1.4 g (83%) of Z-Ser-(*O*-*t*-Bu)-Lys(BOC)-2-cyclohexylethylamide. A solution of this dipeptide (0.19 g, 0.3 mmol) in MeOH (6 mL) containing acetic acid (0.1 mL) was hydrogenated in the presence of 5% palladium on carbon (0.05 g) at atmospheric pressure for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford **25**: ^{1}H NMR (CD_3OD) δ 4.35 (t, Ser-CH, J = 6.3 Hz, 1H), 4.01 (m, Lys-CH, 1H), 3.8 and 3.65 (dd, Ser β-CH_2, J = 4.2, 6.2 Hz, 2H), 3.2 (m, 2H), 3.02 (t, J = 6.9 Hz), 1.7 (m, 7H), 1.6−1.2 (m, 2s, 28H), 0.95 (m, 2H); MW $C_{26}H_{50}N_4O_5$ calcd 499.3859 (M + H), found: 499.3855 (M + H, HRFABMS). Amino acid analysis: Ser 0.99 (1.00); Lys 1.01 (1.00).

(11-Aminoundecanoyl)-Ser-Lys-2-cyclohexylethylamide (17e). A solution containing *N*-BOC-11-aminoundecanoic acid[13] (0.15 g, 0.5 mmol) and hydroxybenzotriazole (HOBt, 0.08 g, 0.52 mmol) in dichloromethane (3.00 mL) and dimethylacetamide (0.5 mL) was cooled to 0 °C, and DCC (0.1 g, 0.5 mmol) was added. After 1 h of stirring, the reaction mixture was filtered, and the filtrate was added to a solution of **25** in dimethylacetamide (1.0 mL) containing *N*-methylmorpholine (0.05 mL). The resulting mixture was stirred at room temperature for 48 h, and the solvents were distilled off under vacuum. The residue was partitioned between 0.5 N NaOH (10 mL) and EtOAc (25 mL) and filtered. The organic phase was washed successively with water (2 × 10 mL), 5% citric acid (2 × 10 mL), and water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The resulting substance was dissolved in EtOAc, precipitated with ether, and filtered to give 0.15 g of a pale yellow powder which was deprotected by stirring with trifluoroacetic acid (2.0 mL) for 3 h. After the removal of trifluoroacetic acid under reduced pressure, the residue was purified by reverse-phase chromatography to give **17e** (80 mg) as a white powder: ^{1}H NMR (CD_3OD) δ 4.28 (m, 2H), 3.75 (m, 2H), 3.1 (t, J = 7.2 Hz, 2H), 2.8 (m, 4H), 2.2 (t, J = 7.2 Hz, 2H), 1.2−2 (m, 35 H); MW $C_{28}H_{55}N_5O_4$ calcd 526.4333, found 526.4357 (M + H, HRFABMS). Amino acid analysis: Ser 1.00 (1.00); Lys 1.00 (1.00).

Methyl *p*-Iodophenylacetate (28a). A solution of *p*-iodophenylacetic acid (**27**, 5.2 g, 0.02 mol) and 4-(dimethylamino)pyridine (0.25 g, 0.002 mol) in dichloromethane (40 mL) and methanol (3.2 mL) was cooled to 0 °C, and a solution of DCC (4.32 g, 0.021 mol) was added dropwise over a period of 15 min. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 16 h and then was filtered. The filtrate was diluted with dichloromethane (40 mL), washed with 5% citric acid (4 × 25 mL) and water (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residual liquid was purified by flash column chromatography on silica gel, eluting with 20% EtOAc in hexane to give the desired methyl ester[16] **28a** (4.5 g, 82%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 2H), 3.69 (s, 3H), 7.01 (2H, J = 8.4 Hz), 7.64 (d, 2H, J = 8.4 Hz); FABMS m/z = 283 (M + Li).

Methyl 4-(6-Hydroxy-1-hexynyl)phenylacetate (29b). To a solution of 5-hexyn-1-ol (0.27 g, 2.75 mmol) and methyl *p*-iodophenylacetate (**28a**, 0.5 g, 1.8 mmol) in acetonitrile (5 mL) at 0 °C was added triethylamine (0.43 g, 4.3 mmol), followed by the addition of bis(triphenylphosphine)palladium-(II) chloride (0.1 g, 0.14 mmol) and CuI (0.025 g). The reaction mixture was stirred at 0 °C under an argon atmosphere for 30 min and then at room temperature for 3 h. The dark, colored reaction mixture was concentrated under reduced pressure, and the residue was partitioned between 5% citric acid (50 mL) and EtOAc (50 mL). The organic phase was washed with 5% citric acid (3 × 15 mL) and water, dried (Na_2SO_4), and concentrated. The resulting material was purified by flash column chromatography on silica gel, eluting with 50% EtOAc in hexane to afford **29b** (0.36 g, 80%) as an orange liquid: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 1H) 2H), 7.19 (d, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 8.1 Hz); MW $C_{15}H_{18}O_3$ calcd 247.1334 (M + H), found 247.1326 (M + H, HRFABMS).

Methyl 4-(6-Hydroxyhexyl)phenylacetate (30b). A solution of **29b** (0.5 g, 2 mmol) in methanol (10 mL) was hydrogenated in the presence of 5% Pd/C (0.15 g) at 20 psi for 4 h. The catalyst was removed by filtration, the filtrate was concentrated, and the resulting material was dried in vacuo to give the titled compound **30b** (0.43 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 1H, J = 5.7 Hz), 3.69 (s, 3H), 7.15 (q, 4H); MW $C_{15}H_{22}O_3$ calcd 251.1648 (M + H), found 251.1631 (M + H, HRFABMS).

Methyl 4-(6-Iodohexyl)phenylacetate (31b). To a solution of **30b** (0.4 g, 1.6 mmol) in dry dichloromethane (15 mL) was added a solution of the methyltriphenoxyphosphonium iodide (1.2 g, 2.65 mmol) in dichloromethane (15 mL), and the resulting mixture was stirred at room temperature for 3 h under argon. The reaction was quenched by the addition of methanol (3 mL) and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL), washed successively with cold 0.2 N NaOH (2 × 20 mL), water (2 × 25 mL), and saturated NaCl (2 × 50 mL), dried over $MgSO_4$, and concentrated. The crude material thus obtained was purified by flash column chromatography on silica gel, eluting with 15% EtOAc in hexane to give 0.44 g (72%) of the iodo ester **31b** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 2H) 1.4 (m, 4H), 1.80 (m, 2H), 3.18 (t, 2H, J = 6.9 Hz), 2.62 (t, 2H, J = 7.8 Hz), 3.59 (s, 2H), 3.69 (s, 3H), 7.17 (AB q, 4H, J = 8.1); MW $C_{13}H_{21}O_2I$ calcd 333.0351 (M + H), found 333.0347 (M + H, HRFABMS).

Methyl 4-(6-Azidohexyl)phenylacetate (32b). A mixture of the iodo ester **31b** (0.4 g, 1.11 mmol), sodium azide (0.15 g, 2.3 mmol), and 18-crown-6 (0.1 g, 0.38 mmol) in dimethylformamide (3.00 mL) was stirred at room temperature for 16 h under an argon atmosphere. The DMF was distilled away in vacuo, and the residue was partitioned between EtOAc (20 mL) and water (10 mL). The organic phase was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The resulting substance was purified by flash column chromatography on silica gel, eluting with 15% EtOAc in hexane to afford the azido ester **32b** (0.23 g, 75%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 2H), 1.59 (m, 2H), 2.6 (t, 2H), 3.25 (t, 2H), 3.59 (s, 2H), 3.65 (m, 2H), 3.69 (s, 3H), 7.15 (q, 4H); MW $C_{15}H_{21}N_3O_2$ calcd 276.1721 (M + H), found 276.1712 (M + H, HRFABMS).

Methyl 4-(*N*-BOC-6-aminohexyl)phenylacetate (33b). The azido ester **32b** (0.22 g, 0.8 mmol) was dissolved in MeOH (10 mL) containing acetic acid (0.1 mL) and hydrogenated in the presence of 5% Pd/C (0.05 g) at 40 psi for 3 h. The palladium catalyst was removed by filtration, and the filtrate

was concentrated under reduced pressure. The resulting substance (0.2 g) was dissolved in dichloromethane (5.00 mL), di-*tert*-butyl dicarbonate[19] (0.2 g, 0.92 mmol) and triethylamine (0.11 g, 1.1 mmol) were added, and the mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure, and the product was purified by flash column chromatography on silica gel, eluting with 20% EtOAc in hexane to give the titled *N*-BOC-protected ester **33b** (0.16 g, 57%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.7−1.3 (s over m, 17H), 2.6 (m, 2H), 3.1 (m, 2H), 3.59 (s, 2H), 3.69 (s, 3H), 7.15 (m, 4H); MW $C_{20}H_{31}NO_4$ calcd 350.2331 (M + H), found 350.2315 (M + H, HRFABMS).

4-(*N*-BOC-6-aminohexyl)phenylacetic Acid (34b). A mixture of the ester **33b** (0.15 g, 0.43 mmol) in THF (0.5 mL) and LiOH (1.0 M, 1.5 mL) was stirred at room temperature under an argon atmosphere. After 2 h, the reaction mixture was diluted with water (5 mL), acidified with 5% citric acid, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The resulting material was dried in a desiccator to give the acid **34b** (0.14 g, 97%): ^{1}H NMR ($CDCl_3$) δ 1.7−1.2 (s over m, 17H), 2.6 (m, 2H), 3.1 (m, 2H), 3.59 (s, 2H), 3.61 (s, 2H), 7.14 (m, 4H); MW $C_{19}H_{29}NO_4$ calcd 336.2176 (M + H), found 336.2154 (M + H, HRFABMS).

(4-(6-Aminohexyl)phenylacetyl)-Ser-Lys-2-cyclohexylethylamide, Trifluoroacetate (26b). The *N*-BOC-protected acid **34b** (0.12 g, 0.36 mmol) was dissolved in a mixture of dichloromethane (3 mL) and dimethylacetamide (0.5 mL), HOBt (0.058 g, 0.38 mmol) and DCC (0.077 g, 0.37 mmol) were added, and the mixture was stirred at 0 °C. After 1.5 h, the mixture was filtered, and the filtrate was added to a solution of the dipeptide amine **25** in dimethylacetamide (1 mL) containing *N*-methylmorpholine (0.046 g, 0.46 mmol), and the mixture was stirred at room temperature for 48 h. The solvents were distilled in vacuo, and the residue was stirred with EtOAc (15 mL) and cold 0.25 N NaOH (10 mL) for 15 min. The organic phase was washed successively with water, 5% citric acid (2 × 10 mL), and brine, dried, and concentrated under reduced pressure. The resulting material was triturated with ether−hexane (1:1 v/v) and filtered. The solid (0.017 g) thus obtained was treated with trifluoroacetic acid (1.8 mL) and anisole (0.2 mL) and stirred at room temperature for 3.5 h. The solvents were removed under reduced pressure, and the residue was purified by HPLC to give the desired product **26b** (0.065 g) as an amorphous hygroscopic substance: ^{1}H NMR (CD_3OD) δ 0.92 (m, 2H), 1.85−1.1 (m, 24H), 1.92 (m, 1H), 2.63 (t, 2H, J = 7.5 Hz), 2.9 (q, 4H, J = 7.5 Hz), 3.17 (m, 2H), 3.58 (s, 2H), 3.72 (AB q, 1H), 4.36 (2H), 7.4−7.05 (m, 4H); MW $C_{31}H_{53}N_5O_4$ calcd 560.4176 (M + H), found 560.4139 (M + H, HRFABMS). Amino acid analysis: Ser 1.0 (1.00); Lys 1.0 (1.00).

4-(*N*-BOC-5-aminopentyl)phenylacetic Acid (34a). Prepared in a similar manner as described for compound **34b**: yield 86%; colorless liquid; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.45 (m, 2H), 1.5 (m, 2H), 1.6 (m, 2H), 2.6 (t, 2H, J = 7.8 Hz), 3.1 (m, 2H, J = 7.2 Hz), 3.59 (s, 2H), 3.62 (s, 3H), 7.15 (q, 4H, J = 8.4 Hz); MW $C_{18}H_{27}NO_4$ calcd 328.2100 (M + Li), found 328.2105 (M + Li, HRFABMS).

(4-(5-Aminopentyl)phenylacetyl)-Ser-Lys-2-cyclohexylethylamide (26a). Prepared in a similar manner as described for compound **26b**: yield 43%; white amorphous powder; ^{1}H NMR (CD_3OD) δ 0.92 (m, 2H), 1.8−1.1 (m, 22H), 1.92 (m, 1H), 2.61 (t, 2H), 2.89 (m, 4H), 3.18 (m, 2H), 3.56 (s, 2H), 3.72 (m, 1H), 3.85 (m, 1H), 4.35 (m, 2H), 7.15 (m, 4H); MW $C_{30}H_{51}N_5O_4$ calcd 546.4019 (M + H), found 546.4014 (M + H, HRFABMS). Amino acid analysis: Ser 1.02 (1.00); Lys 0.98 (1.00).

4-(*N*-BOC-8-aminooctyl)phenylacetic Acid (34c). This compound was prepared in a similar manner as described for **34b**: yield 82%; white powder; ^{1} H NMR ($CDCl_3$) δ 1.27 (m, 8H), 1.44 (s over m, 11H), 1.58 (m, 2H), 2.58 (t, 2H, J = 7.8 Hz), 3.08 (m, 2H), 3.61 (s, 2H), 7.15 (q, 4H, J = 8.1 Hz); MW $C_{21}H_{34}NO_4$ calcd 370.2570 (M + Li), found 370.2567 (M + Li, HRFABMS).

(4-(8-Aminooctyl)phenylacetyl)-Ser-Lys-2-cyclohexylethylamide (26c). This compound was prepared in a similar manner as described for **26b**: ^{1}H NMR (CD_3OD) δ 0.94 (m, 2H), 1.5−1.1 (m, 16H), 1.65 (m, 12H), 1.92 (m, 1H), 2.86 (q, 4H, J = 7.2 Hz), 2.59 (t, 2H, J = 7.2 Hz), 3.19 (m, 2H), 3.56 (s, 2H), 3.77 (dd, 1H), 3.85 (dd, 1H), 4.35 (m, 2H), 7.15 (q, 4H, J = 8.0 Hz); MW $C_{33}H_{57}N_5O_4$ calcd 588.4489 (M + H), found 588.4485 (M + H, HRFABMS). Amino acid analysis: Ser 1.03 (1.00); Lys 0.97 (1.00).

2-[4-(*N*-BOC-6-aminohexyl)phenyl]propionic Acid (34d). The title compound was prepared as described for **34b** starting from 5-hexyn-1-ol and racemic methyl 2-(*p*-iodophenyl)propionate:[17] ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 4H), 1.44 (s over m, 11H), 1.49 (d, 3H, J = 7.2 Hz), 1.6 (m, 2H), 2.55 (t, 2H, J = 7.1 Hz), 3.18 (br, 2H), 3.71 (q, 1H, J = 7.2 Hz), 4.5 (br, 1H), 7.13 (d, 2H, J = 8.1 Hz), 7.2 (d, 2H, J = 8.1 Hz); MW $C_{20}H_{31}NO_4$ calcd 356.2413 (M + Li), found 356.2376 (M + Li, HRFABMS).

[2-[4-(6-Aminohexyl)phenyl]propionyl]-Ser-Lys-2-cyclohexylethylamide (48). Prepared by coupling **34d** with **25** followed by deprotection as described for **26b**: ^{1}H NMR (CD_3OD) δ 0.9 (m, 2H), 1.8−1.1 (m, 26H), 1.9 (m, 2H), 2.58 (t, 2H, J = 7.8 Hz), 2.87 (m, 4H), 3.18 (m, 2H), 3.8−3.6 (m, 3H), 4.25 (m, 2H), 7.11 (d, 2H, J = 7.8 Hz), 7.24 (m, 2H); MW $C_{32}H_{55}N_5O_4$ calcd 574.4332 (M + H), found 574.4357 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

(3-(5-Aminopentyl)phenylacetyl)-Ser-Lys-2-cyclohexylethylamide (36). This compound was prepared as described for **26b** but starting from *m*-iodophenylacetic acid. ^{1}H NMR (CD_3OD) δ 0.96 (m, 2H), 1.53−1.1 (m, 10H), 1.82−1.54 (m, 12H), 1.94 (m, 1H), 2.66 (t, 2H, J = 7.5 Hz), 2.91 (m, 4H), 3.18 (m, 2H), 3.57 (s, 2H), 3.72 (m, 1H), 3.85 (m, 1H), 4.36 (m 2H), 7.42−7.05 (m, 4H); MW $C_{30}H_{51}N_5O_4$ calcd 546.4019 (M + H), found 546.4036 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

4-[(*N*-BOC-amino)methyl]iodobenzene (40). A mixture containing 4-(aminomethyl)iodobenzene (**39**, 1.5 g, 6.4 mmol) and di-*tert*-butyl dicarbonate[19] (1.5 g, 6.8 mmol) in dichloromethane (25 mL) was stirred at room temperature for 16 h. The solution was diluted with dichloromethane (25 mL), washed with 5% citric acid (2 × 20 mL) and brine (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting material was triturated with hexane, and the precipitate was filtered, washed with hexane, and dried in a desiccator in vacuo to afford the titled product **40** (1.7 g, 80%) as a pale yellow powder: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 4.24 (d, 2H, J = 6.0 Hz), 4.82 (br, 1H), 7.02 (d, 2H, J = 8.1 Hz), 7.64 (d, 2H, J = 8.1 Hz); MW $C_{12}H_{16}NO_2I$ calcd 334.0304 (M + H), found 334.0286 (M + H, HRFABMS)

7-[4-[(*N*-BOC-amino)methyl]phenyl]hept-6-ynoic Acid (41). To a solution of 6-heptynoic acid (0.4 g, 3.2 mmol) and **40** (1.0 g, 3 mmol) in acetonitrile (5.00 mL) were added $(PPh_3)_2PdCl_2$ (0.2 g) and CuI (0.04 g), and the mixture was stirred at 5 °C for 30 min. After being stirred at room temperature for 4 h, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc (25 mL), washed successively with 5% citric acid (2 × 10 mL) and water (2 × 20 mL), and dried (Na_2SO_4). The solution was concentrated under reduced pressure, and the resulting orange material was purified by flash column chromatography on silica gel, eluting with 50% EtOAc in hexane to afford the titled compound **41** (0.47 g, 47%) as a white powder: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.67 (m, 2H), 1.8 (m, 2H), 2.43 (m, 4H), 4.28 (d, 2H, J = 4.8 Hz), 4.82 (br, 1H), 7.18 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.0 Hz); MW $C_{19}H_{25}NO_4$ calcd 332.1862 (M + H), found 332.1844 (M + H, HRFABMS).

[7-[4-(Aminomethyl)phenyl]-6-heptynoyl]-Ser-Lys-2-cyclohexylethylamide (37). This compound was prepared by coupling **41** with **25** followed by deprotection as described for **26b**: ^{1}H NMR (CD_3OD) δ 0.95 (m, 2H) 1.9−1.4 (m, 20H), 1.95 (m, 1H), 2.33 (t, 2H, J = 8.9 Hz), 2.46 (t, 2H, J = 8.9 Hz), 2.92 (t, 2H, J = 8.9 Hz), 3.2 (m, 2H), 3.75 (m, 1H), 3.85 (m, 1H), 4.1 (s, 2H), 4.35 (m, 2H), 7.29 (m, 4H); MW $C_{31}H_{49}N_5O_4$ calcd 556.3863 (M + H), found 556.3881 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

7-[4-[(*N*-BOC-amino)methyl]phenyl]heptanoic Acid (42). The acetylenic acid[24] **41** (0.2 g, 0.6 mmol) was dissolved in EtOAc (10 mL) and hydrogenated at 40 psi in the presence of 5% Pd/C (0.15 g) for 3.5 h. The suspension was filtered, the filtrate was concentrated under reduced pressure, and the

resulting substance was dried in a desiccator in vacuo to afford the titled compound **42** as a white powder: ^{1}H NMR ($CDCl_3$) δ 1.34 (m, 4H), 1.46 (s, 9H), 1.62 (m, 4H), 2.33 (t, 2H, J = 8.1 Hz), 2.58 (t, 2H, J = 8.1 Hz), 4.28 (d, 2H, J = 4.8 Hz), 4.82 (br, 1H), 7.14 (q, 4H); MW $C_{19}H_{29}NO_4$ calcd 342.2257 (M + Li), found 342.2256 (M + Li, HRFABMS).

[7-[4-(Aminomethyl)phenyl]heptanoyl]-Ser-Lys-2-cyclohexylethylamide (38). This compound was prepared by coupling **42** with **25** followed by deprotection as described for **26b**: yield 30%; ^{1}H NMR (CD_3OD) δ 0.85 (m, 2H), 1.7−1.1 (m, 24H), 1.88 (m, 1H), 2.19 (t, 2H, J = 7.2 Hz), 2.57 (t, 2H, J = 7.2 Hz), 2.85 (t, 2H, J = 7.2 Hz), 3.13 (m, 2H), 3.65 (m, 1H), 3.76 (m, 1H), 3.99 (s, 2H), 4.29 (m, 2H), 7.27 (d, 2H, J = 7.8 Hz); MW $C_{31}H_{53}N_5O_4$ calcd 560.4176 (M + H), found 560.4161 (M + H, HRFABMS). Amino acid analysis: Ser 1.03 (1.00); Lys 0.97 (1.00).

Methyl 4-Ethynylphenylacetate (45). This compound was prepared by coupling **28a** with (trimethylsilyl)acetylene as described for **29b**, followed by desilylation with tetrabutylammonium fluoride in acetonitrile to give **45**, which was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz), 3.7 (s, 3H), 3.63 (s, 2H), 3.06 (s, 1H); FABMS m/z = 175 (M + H).

4-[[4-[(*N*-BOC-amino)methyl]phenyl]ethynyl]phenylacetic Acid (46). To a solution of *p*-[(*N*-BOC-amino)methyl]-iodobenzene (**40**, 0.63 g, 1.9 mmol) and methyl 4-ethynylphenylacetate (**45**, 0.3 g, 1.72 mmol) in acetonitrile (5.0 mL) were added triethylamine (0.29 g, 2.85 mmol), bis(triphenylphosphine)palladium(II) chloride (0.13 g, 0.17 mmol), and CuI (0.05 g), and the mixture was stirred at 10 °C for 30 min. After 1 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (25 mL) and 5% citric acid (25 mL). The organic phase was washed with water (2 × 20 mL), dried (Na_2SO_4), and concentrated. The resulting substance was purified by flash column chromatography on silica gel, eluting with 20% EtOAc in hexane to afford 0.55 g (77%) of the coupled ester. This ester (0.45 g, 1.19 mmol) was stirred with a mixture of 1 M LiOH (2.0 mL) and THF (2.0 mL) at room temperature for 1.5 h. The reaction mixture was diluted with water (15 mL), cooled, acidified with 5% citric acid, and then extracted with EtOAc (3 × 15 mL). The organic extracts were combined, washed with water (2 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting material was purified by crystallization from EtOAc/hexane to afford 0.31 g (71%) of the acid **46** as a pale yellow powder: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 3.67 (s, 2H), 4.30 (br, 2H), 7.26 (m, 4H), 7.49 (m, 4H); MW $C_{22}H_{23}NO_4$ calcd 366.1705 (M + H), found 366.1711 (M + H, HRFABMS).

[4-[[4-(Aminomethyl)phenyl]ethynyl]phenylacetyl]-Ser-Lys-2-cyclohexylethylamide(43). Prepared by coupling **46** with **25** followed by deprotection as described for **26b**: ^{1}H NMR (CD_3OD) δ 0.95 (m, 2H), 1.8−1.2 (16H), 1.98 (m, 1H), 2.88 (t, 2H, J = 7.2 Hz), 3.83 (m, 1H), 3.18 (m, 2H), 3.75 (m, 1H), 3.64 (s, 2H), 4.14 (s, 2H), 4.36 (m, 2H), 7.33 (d, 2H, J = 8.1 Hz), 7.47 (m, 4H), 7.58 (d, 2H, J = 8.1 Hz); MW $C_{34}H_{47}N_5O_4$ calcd 590.3706 (M + H), found 590.3685 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

4-[[4-[(*N*-BOC-amino)methyl]phenyl]ethyl]phenylacetic Acid (47). This compound was prepared by the hydrogenolysis of **46** as described for **30b**: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.89 (s, 4H), 3.62 (s, 2H), 4.32 (br d, 2H), 4.8 (br, 1H), 7.14 (m, 8H); MW $C_{22}H_{27}NO_4$ calcd 376.2100 (M + Li), found 376.2153 (M + Li, HRFABMS).

[4-[[4-(Aminomethyl)phenyl]ethyl]phenylacetyl]-Ser-Lys-2-cyclohexylethylamide (44). The titled compound was prepared by coupling **47** with **25** followed by deprotection as described for **26b**: ^{1}H NMR (CD_3OD) δ 0.91 (m, 2H), 1.8−1.1 (m, 16H), 1.93 (m, 1H), 2.88 (m, 6H), 3.18 (m, 2H), 3.55 (s, 2H), 3.72 (m, 1H), 3.83 (m, 1H), 4.06 (s, 2H), 4.32 (m, 2H), 7.15 (dd 4H, J = 8.1 Hz), 7.28 (dd 4H, J = 8.1 Hz); MW $C_{34}H_{51}N_5O_4$ calcd 594.4019 (M + H), found 594.4007 (M + H, HRFABMS). Amino acid analysis: Ser 0.97 (1.00); Lys 1.03 (1.00).

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(12) Abbreviations: (a) Bn, benzyl; (b) BOC, *tert*-butoxycarbonyl; (c) Z, carbobenzyloxy; (d) DIEA, diisopropylethylamine; (e) mBHA, 4-methylbenzhydrylamine; (f) Su, *N*-hydroxysuccinimde; (g) TFA, trifluoroacetic acid.

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(21) Except where noted in the tables, all of the IC_{50} and $K_{i(app)}$ values reported in the text are measured against *C. albicans* NMT. The reported IC_{50}s represent an average of two or more determinations. All of the K_is are reported as apparent inhibition constants ($K_{i(app)}$), competitive versus the peptide substrate GNAASARR-NH_2, as described previously in ref 8c.

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