Design and Synthesis of Novel FKBP Inhibitors

James R. Hauske,* Peter Dorff, Susan Julin, Joseph DiBrino, Robin Spencer, and Rebecca Williams

Central Research Division, Pfizer Inc, Groton, Connecticut 06340

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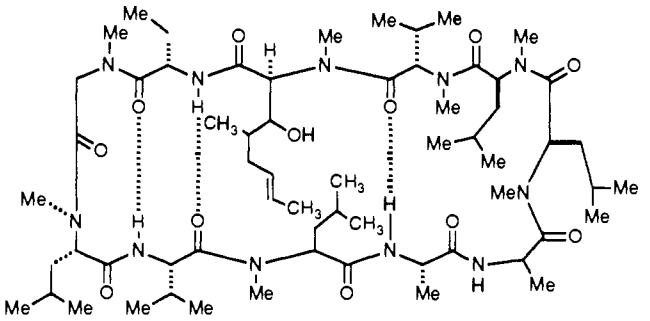
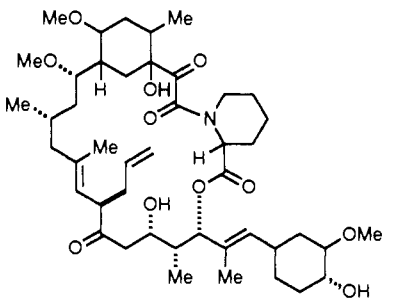
Small molecule FKBP inhibitors were prepared with inhibitory activity ranging from micromolar to nanomolar. The design of these inhibitors derives from a structural analysis of the substrates for FKBP and cyclophilin. As a consequence of this analysis two key observations were made, namely: (1) amino ketone moieties are suitable as FKBP recognition elements at the P_1-P_1' site and (2) the P_3'-P_4' site will accept a *trans*-olefin as a suitable mimetic of a peptide moiety. The preparation of these non-peptide inhibitors is readily accomplished by a protocol which includes the synthesis of chiral propargylic amines and their subsequent conversion into vinyl zirconium reagents.

Introduction

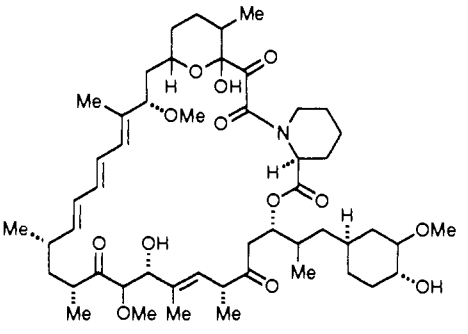
The immunophilins are a family of phylogenically conserved binding proteins possessing peptidyl prolyl isomerase activity (rotamase).[1,2] Since these binding proteins are not localized solely to lymphoid tissue, but rather, they are widely disseminated over a variety of tissue types, many researchers have proposed that the immunophilins are fundamentally important in regulating cellular metabolic events.[3] Although the exact nature of such regulatory phenomena has not been fully elucidated, it is most interesting that the potent immunosuppressants cyclosporin A, FK506, and rapamycin (Figure 1) bind two distinct immunophilins, namely, cyclophilin[4] and FK binding protein (FKBP),[5,6] respectively; furthermore, the immunosuppressants inhibit the peptidyl prolyl isomerase activity of their respective targets. Also, it has been demonstrated that cyclophilin and FKBP are necessary mediators of the cytotoxic effects of cyclosporin A, FK506, and rapamycin in lower eukaryotes.[6,7] Although disruption of the folding processes of cellular targets would provide a sensitive means of controlling cellular metabolic events,



CsA



FK506



Rapamycin

Figure 1. Structures of potent immunophilin inhibitors.

it has been demonstrated that the rotomase inhibitory activity of cyclosporin A[8] and FK506[9] is not a sufficient

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condition for potent immunosuppression. In fact, recently it was shown that calcineurin, a calcium-dependent phosphatase, is the common target for both the cyclosporin A–cyclophilin complex and the FK506–FKBP complex.[10] Thus, it is not possible to invoke a *direct* role for the immunophilins in regulating a signaling pathway in T- and B-lymphocytes.[11] However, an alternative role for the immunophilins might well relate to their ability to impart conformational restrictions to bound inhibitors. The resulting bound inhibitor conformations would not necessarily be identical to the lowest free energy solution conformation of the unbound inhibitor. The conformational effects imparted to the inhibitor by the binding protein may require the immunophilin–inhibitor complex to behave as the initiator of the events that ultimately control signaling pathways in specific target tissues. Support for such a notion is derived from the recently reported solution NMR study of free and bound cyclosporin A,[12] which showed two distinctly different lowest free energy conformations. Since subtle conformational effects of inhibitor–immunophilin complexes could be responsible for the ultimate control of significant cellular metabolic events, we became interested in the design and synthesis of small-molecule immunophilin inhibitors. These targets might be very useful probes for more facile NMR determinations of bound inhibitor complexes, which may ultimately also provide insight into the control of cellular metabolic events. This work details the design and synthesis of small-molecule immunophilin inhibitors, specifically, FKBP inhibitors.

Results and Discussion

Although the isomerase activity of the immunophilins is not directly linked to immunosuppressive activity, it is likely that the binding site for biologically significant immunophilin–inhibitor complexes and the isomerase catalytic site overlap. Therefore, we initially considered the minimum requirements for recognition at the isomerase catalytic site. For example, it has been demonstrated that the transition state for the isomerization of peptidyl prolyl bonds by the immunophilin, FKBP, is approximated by a twisted amide,[9] and that a suitable mimic of a distorted amide transition state has been achieved by FK506, as well as its structural analog rapamycin, by virtue of the amido ketone moiety of the latent tricarbonyl segment; furthermore, it has also been demonstrated that peptide *substrates* of FKBP,[9,13] as well as cyclophilin,[14] define a twisted amide transition state upon binding. A twisted amide requires that the resonance between the nitrogen atom and the carbonyl moiety is disrupted and, therefore, begins to approximate an amino ketone. Thus, we considered *amino ketones* as reasonable recognition elements for FKBP inhibitors.

P_1–P_1' Recognition Element

The three-dimensional nature of the active site of FKBP has been defined by solid state and NMR solution methods[15] and, much like the binding pocket of cyclophilin,[12] the binding protein for the immunosuppressant cyclosporin A, the FKBP active site is highly lipophilic, in that it is lined with an extensive array of aromatic residues. Although FKBP and cyclophilin are distinct proteins, they are both isomerases and, as such, it is not surprising that the active sites of both proteins have similar electronic requirements. Thus, we began our search for small molecule inhibitors of FKBP by synthesizing targets that incorporated amino ketone recognition elements terminated by lipophilic moieties. Initially, since it has been proposed that the latent tricarbonyl region of FK506 is a recognition element for binding to FKBP,[9] we prepared small molecule FKBP inhibitors containing an *amido ketone* for a direct comparison to the proposed *amino ketone* segments. The synthesis of the desired targets is outlined in Scheme I, and in all respects the synthesis proceeds in a straightforward manner.

The direct comparisons of an amido ketone moiety versus an amino ketone moiety as recognition elements demonstrate that the amino ketone recognition moiety imparts improved inhibitory properties [Table I, **3** ($IC_{50} \gg 100\,\mu M$); **5** ($IC_{50} = 60\,\mu M$)] to small molecule inhibitors. Furthermore, amino ketone moieties with aryl ketone substituents at the P_1 position not only are superior to the corresponding cyclohexyl substituents (compare, for example, compounds **5**, **6**, and **7** in Table I) but also are superior to P_1 moieties containing polar functionality attached to sp^3-hybridized centers proximal to the carbonyl substituent (compare compounds **6** and **8** in Table I). We next assessed the requirements of the P_1' position. Replacement of proline by homoproline imparts a dramatic effect of FKBP inhibition (compare compounds **4** and **9**, as well as compounds **6** and **10**). Presumably, the well-defined conformational bias of the six-membered homoproline moiety, which is most easily rationalized in terms of A(1,3) strain, is responsible for the observed biological result.[9,15]

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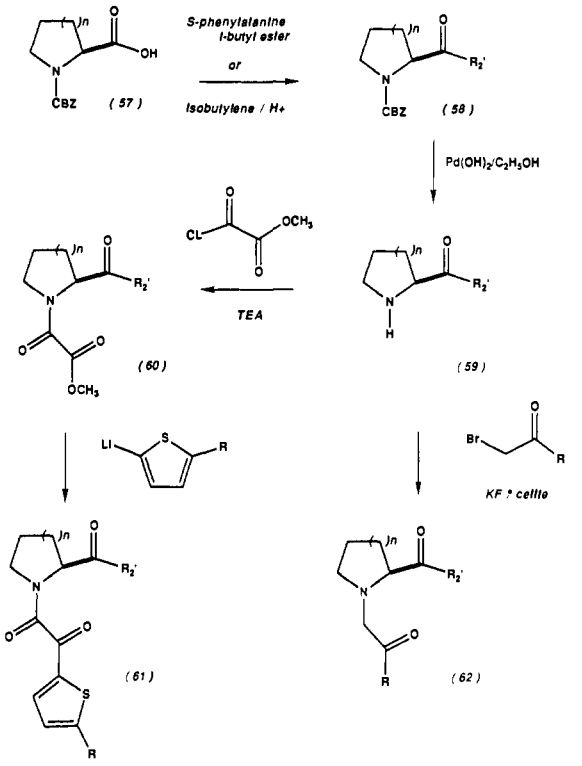
Scheme I. Synthetic Approach to the Amino Amides and the Amino Ketones

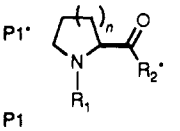


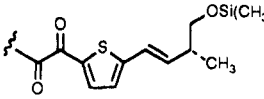
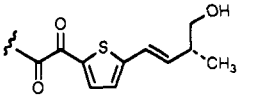
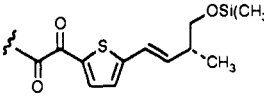
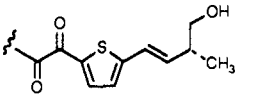
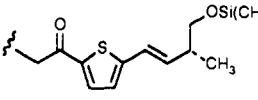
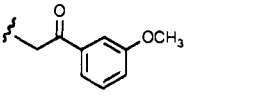
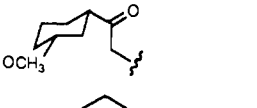
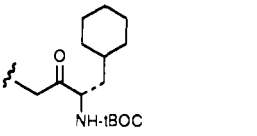
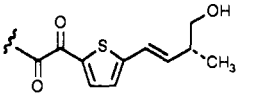
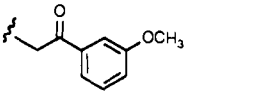
Evaluation of the P_2' Position

Since FK506 and its congeners, as well as some of the peptide substrates of FKBP have an alkyl side chain terminated by a six-membered ring overlapping the P_2' position,[9,12-14] we incorporated similar moieties into our synthetic inhibitors. Initially, we assessed the effect that various substituents, as well as stereochemistry, at the P_2' chiral center would have on FKBP inhibition. Table II lists the specific examples that were studied.

The comparison of the benzyl-substituted compounds, **10** and **11**, demonstrates that the natural (*S*) stereochemistry of the P_2' position imparts greatly improved biological activity [Table II, **11** (81 μM) vs **10** (3 μM)]. Also, extension of the P_2' side chain by one additional methylene unit destroys the FKBP inhibitory activity, since benzyl substituents are superior to phenylethyl substituents [Table II, **10** (3 μM) vs **12** (>100 μM)]. The corresponding hexahydro derivatives, **13** and **14**, are also very poor inhibitors. Similarly, when the benzyl moiety is replaced by a heteroaromatic [Table II, compare compounds **10** (3 μM), **15** (22 μM), and **16** (23 μM)] substituent, the inhibitory activity is reduced. Since the binding pocket of FKBP has a number of electron-rich aromatic moieties,[2,9,15] we replaced the benzyl substituent at the P_2' position with an electron-deficient aromatic substituent (R_2' = *p*-NO_2-phenyl, **17**) hoping to maximize an attractive, stacking interaction. Inspection of Table II also shows that compound **17** is a significantly less potent inhibitor compared to compound **10** (27 μM vs 3 μM). Finally, we investigated the effects of branched chain substituents at the P_2' position. Replacement of the P_2' benzyl substituent by an isopropyl moiety (compounds **10** and **18**) decreases the potency (3 μM vs 83 μM); however, when a 2-butyl substituent is incorporated into the P_2' site (**19**) the potency is not greatly decreased [**10** (3 μM) vs **19** (8 μM)]. Thus, the optimum P_2' substituent is (*S*)-phenylalanine.

Table I. Evaluation of P_1-P_1' Recognition Element



compd no.	*n*	R_1	R_2'	IC_{50} (μM)
1	1		O-*tert*-butyl	≫100
2	1		a	≫100
3	1		Phe-O-*tert*-butyl	~120
4	1		a	~120
5	1		a	60
6	1		a	12
7	1		a	≫100
8	1		a	≫100
9	2		a	9
10	2		a	3

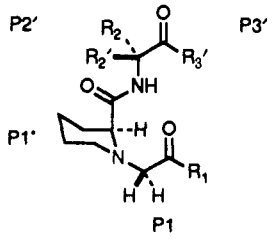
[a] Same as above.

Evaluation of the P_3' Position

Table III lists the various substituents that were incorporated into the P_3' site to probe electronic and steric constraints. Introduction of phenylalanine *tert*-butyl ester at the R_3' position (see Table III, compound **20**, 40 μM) reduces the FKBP inhibitory activity relative to the *tert*-butyl ester (**10**, 3 μM), whereas incorporation of a branched chain alkyl moiety (valine, leucine, and isoleucine, *tert*-butyl esters, **21**–**23**) all retain reasonable potency [**10**, (3 μM), **21** (3 μM), **22** (3 μM), **23** (6 μM)]. The electronic effect was probed by the direct comparison of a hydrophilic substituent, namely, a blocked lysine moiety (**25**, >100 μM), to the corresponding hydrophobic moiety allylalanine (**26**, 12 μM). This comparison minimizes the gross steric distinctions, while maximizing the electronic differences. Clearly, there is a decided preference for a hydrophobic, non-hydrogen bonding moiety.

Since the overall energetic contribution of small molecule inhibitors to the overall binding energy may be related to

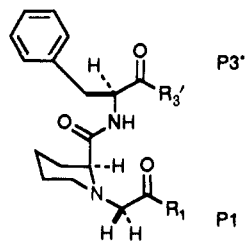
Table II. Evaluation of the P_2' Position



compd no.	R_1	R_2'	R_2	R_3'	IC_{50} (μM)
10	*m*-OCH_3Ph	CH_2Ph	H	O-*tert*-butyl	3
11	*a*	H	CH_2Ph	*a*	81
12	*a*	CH_2CH_2Ph	H	O-isopropyl	>100
13	*a*	CH_2-cyclohexyl	*a*	O-*tert*-butyl	91
14	*a*	CH_2CH_2-cyclohexyl	*a*	O-isopropyl	>100
15	*a*	3-thienyl	*a*	O-*tert*-butyl	22
16	*a*	2-thienyl	*a*	*a*	23
17	*a*	*p*-NO_2PhCH_2	*a*	*a*	27
18	*a*	isopropyl	*a*	*a*	83
19	*a*	2-butyl	*a*	*a*	8

[a] Same as above.

Table III. Evaluation of P_3' Position



compd no.	R_1	R_3'	IC_{50} (μM)
10	*m*-OCH_3Ph	O-*tert*-butyl	3
20	*a*	Phe-O-*tert*-butyl	40
21	*a*	Val-O-*tert*-butyl	3
22	*a*	Leu-O-*tert*-butyl	3
23	*a*	Ileu-O-*tert*-butyl	6
24	*a*	hexahydro-Phe-O-*tert*-butyl	70
25	*a*	ϵ-CBZ-Lys-O-benzyl	>100
26	*a*	allylalanine-O-*tert*-butyl	12
27	β-naphthyl	hexahydro-Phe-O-*tert*-butyl	35
28	β-naphthyl	Val-O-*tert*-butyl	1

the exact substituent composition, we were concerned that the optimization of the P_1 position as described in Table I may be misleading.[16] Therefore, we prepared compound **28**, which incorporates a more lipophilic aryl β-naphthyl moiety. Table III shows that **28** is a slightly more potent [**28** (1 μM) vs **10** (3 μM)] FKBP inhibitor. We conclude from this comparison, that the optimization of the P_1 through P_3' positions in a sequential manner, although not exact, is not very misleading.[17]

Evaluation of the P_4' Position

The optimized P_1–P_3' segment results in an inhibitor (compound **28**, Table III) that includes the hydrophobic residues phenylalanine and valine at the P_2'–P_3' sites, as well as the hydrophobic β-naphthyl terminus at the P_1 site. On the basis of these results, we continued to follow the design elements we utilized to prepare inhibitor **28** and we extended the hydrophobic manifold into the P_4' site. Table IV outlines the selected targets and their corresponding inhibitory activity.

The most striking aspect of the data appearing in Table IV is the activity of compounds **31** and **32** (Table IV, **31** = 1 μM; **32** = 0.3 μM). Clearly, extension of a hydrophobic moiety into the P_4' site improves the inhibitory activity; also, not too surprisingly, when there is no P_1 contribution to the overall recognition and binding, there is no inhibitory activity (compounds **29** and **30**, Table IV). Interestingly, esters are superior to amides as termini for the P_4' site (compare compounds **31** and **32** to compounds **36–42** in Table IV). Apparently, hydrogen bonding is not a *significant* contributor to the overall binding energy at this subsite of the complex. Furthermore, within the ester functionality type there is a severe steric constraint, since the *tert*-butyl moiety (compounds **34** and **35**, Table IV) is inferior to the corresponding methyl substituent (compounds **31** and **32**, Table IV). Finally, when a chiral 1-phenethyl terminus is utilized, there is a slight, but measurable, preference for the *S*-configuration (compare compounds **39–42**, Table IV). Thus, extension of these small molecule inhibitors into the P_5' site does not significantly improve the overall inhibitory activity.

Evaluation of P_3'–P_4' Peptidic Mimics

Since hydrophobic moieties seem preferable at the P′ sites of the FKBP inhibitors, we considered incorporation of a trans double bond spanning the P_3'–P_4' sites. In fact, trans double bonds have long been viewed as suitable *spatial* mimics of the peptide amide linkage, although, in practice, these moieties typically do not prove to be suitable peptide replacements by virtue of their inappropriate, nonpolar electronic properties.[18] However, we viewed the double bond replacement along the P′ sites favorably, since there is a *clear* preference for hydrophobic moieties at these subsites. Initially, we inserted the double bond at the P_2'–P_3' site. Unfortunately, this was not an acceptable substitution, since the inhibitory properties of these compounds were inferior to compound **10**; however, a trans double bond is a suitable surrogate for the P_3'–P_4' amide linkage, since this substitution restores the FKBP inhibitory activity. For example, the allylic acetate **46** (see Table V), which was prepared via the chain extension–reduction protocol[19] outlined in Scheme II, has inhibitory properties that are comparable to more elaborate peptides [compare compounds **10** (3 μM), **28** (1 μM), and **31** (1 μM) vs compound **46** (2 μM)]. We infer from these results that there is a hydrogen bonding requirement for the P_2'–P_3' side, whereas the P_3'–P_4' site simply requires a hydrophobic spacer with the appropriate geometrical constraint. The hydrogen bond requirement at the P_2' site is supported by the recently reported solution NMR and solid state data for FK506 bound to FKBP.[15]

Since the amide linkage of naturally occurring peptides is usually flanked by two sp^3-hybridized carbon atoms, we prepared a variety of substituents not only varying the level of substitution at the sp^3-hybridized "α" carbon locus, but also varying the hybridization state. This was readily

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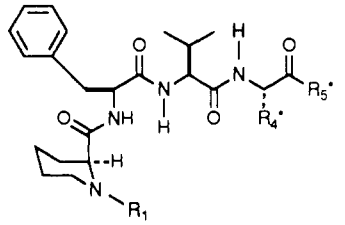
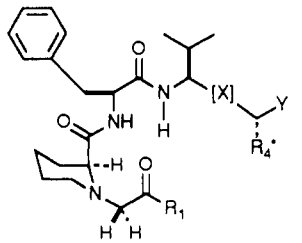
Table IV. Evaluation of P_4' Position



compd no.	R_1	R_4'	R5′	IC_{50} (μM)
29	H	CH_2Ph	OCH_3	≫100
30	CBZ	CH_2Ph	OCH_3	≫100
31	$CH_2(CO)$-*m*-OCH_3Ph	*a*	*a*	1
32	$CH_2(CO)$-β-naphthyl	*a*	*a*	0.3
33	$CH_2(CO)$-biphenyl	*a*	*a*	26
34	$CH_2(CO)$-*m*-OCH_3Ph	*a*	O-*tert*-butyl	20
35	$CH_2(CO)$-β-naphthyl	*a*	O-*tert*-butyl	13
36	*a*	*a*	(*R*)-$NH(CH_3)CH$-α-naphthyl	75
37	*a*	*a*	(*R*)-$NH(CH_3)CHPh$	65
38	$CH_2(CO)$-*m*-OCH_3Ph	*a*	(*R*)-$NH(CH_3)CH$-α-naphthyl	30
39	$CH_2(CO)$-*m*-OCH_3Ph	CH_2Ph	(*R*)-$NH(CH_3)CHPh$	85
40	*a*	*a*	(*S*)-$NH(CH_3)CHPh$	59
41	*a*	*a*	(*R*)-$O(CH_3)CHPh$	23
42	*a*	*a*	(*S*)-$O(CH_3)CHPh$	56

[a] Same as above.

Table V. Evaluation of the P_3'-P_4' Peptidic Mimics



compd no.	R_1	X	R_4'	Y	IC_{50} (μM)
43	*m*-OCH_3Ph	C≡CH	–	–	5
44	*a*	*trans*-CH=CH	=O	OC_2H_5	15
45	*a*	*a*	H	OAc	2
46	β-naphthyl	*a*	*a*	*a*	18
47	*a*	*a*	=O	(*R*)-$NHCH(CH_3)Ph$	35
48	*m*-OCH_3Ph	*a*	*a*	*a*	40
49	*a*	*a*	CH_3	$CH_2C(O)CH_3$	10
50	*a*	*a*	$-CH_2CH_2C(O)CH_2-$		11
51	*a*	*a*	$-CH_2CH_2CH_2C(O)O-$		42
52	*m*-OCH_3Ph	*trans*-CH=CH	H	OC(O)Ph	62
53	*a*	*a*	H	$OC(O)CF_3$	1
54	*a*	*trans*-CH=CHI	–	–	2
55	*a*	*trans*-CH=CH	H	$OCH_2CH=CH_2$	3
56	*a*	C=O[b]	*a*	Ph	14

[a] Same as above. [b] Compound 56 was prepared by Grignard addition to the Weinreb amide of Boc-valine and subsequent chain extension via the N-terminus.

accomplished by elaborating a common, blocked amino aldehyde intermediate. For example, the sp^2-hybridized and the sp-hybridized carbon atoms are introduced via stabilized ylide additions to aldehyde[19,20] (**65**) (see Schemes II and III). The desired branched chain sp^3-hybridized targets are prepared via Ni(II)-catalyzed conjugate addition[21] of the corresponding vinyl zirconium intermediate[22] to a variety of appropriately substituted α,β-unsaturated acceptors (see Scheme III). It is interesting to note that the catalytic $Ni^{\dagger}$(II) species prepared via diakyl aluminum hydride reduction of $Ni(AcAc)_2$[21] is a more facile mediator (yields ranging from 40–75%) of the 1,4-addition process than stoichiometric $Ni(AcAc)_2$ (yields ~10%).

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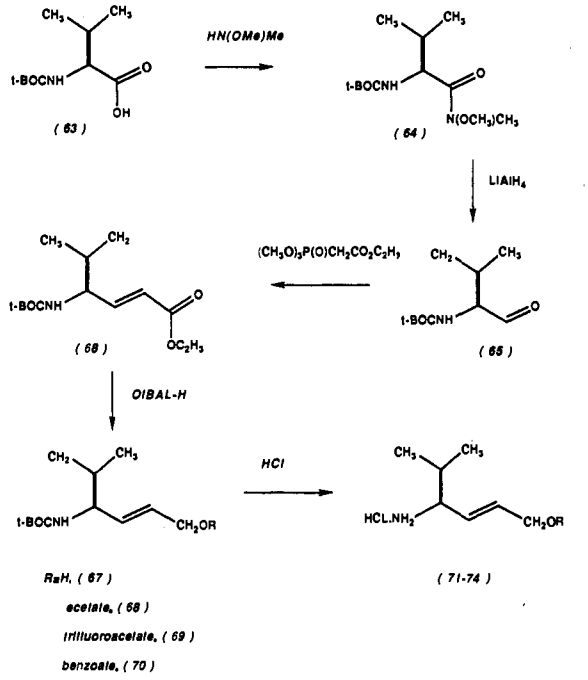
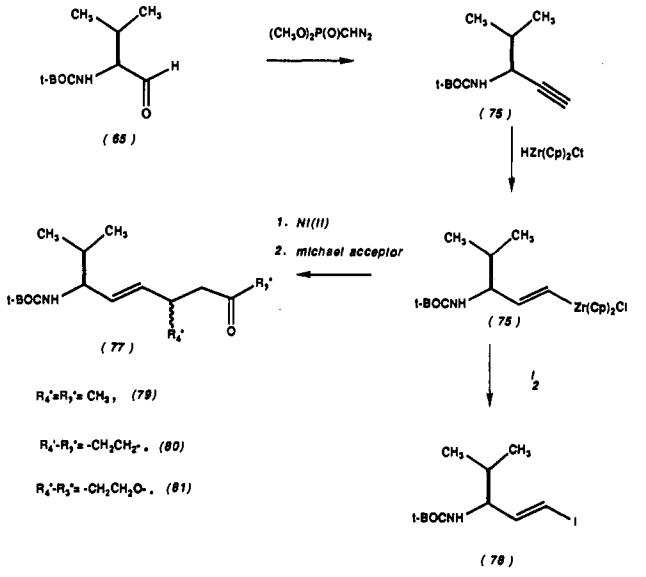
Scheme II. Preparation of Intermediates Incorporated into the P_3'–P_4' Position



Scheme III. Hydrozirconation and Nickel-Catalyzed Chain Extension of Propargyl Amino Moiety



This is a satisfying result, since there are no reports of this coupling being performed on substrates containing propargylic amino[23] substituents. An alternative approach to the carbon–carbon bond formation at the "α" position is the Pd(II)-mediated cross-coupling of the vinyl iodide **78** with substituted organometallics.[24] We successfully utilized $PdCl_2(dppf)$[25] as the Pd(II) source for the coupling of the vinyl iodide **78** with simple Grignard reagents. However, this approach proved less flexible than the Ni(II) approach and, therefore, it was abandoned.

Although the FKBP inhibition data is not for an exhaustive list of P_3'–P_4' peptidic mimics, there are some emerging trends. It is clear that sp^3-hybridized centers proximal to the double bond are preferable to highly polarized sp^2-hybridized centers (compare compounds **44** and **45** in Table V). This result is perhaps not too surprising, since sp^3-hybridized centers are preferred at this site in nature. Also, the more lipophilic ester terminus is superior to the more hydrophilic amide terminus (compare compounds **44**, **46**, and **48**). Once again, the general preference beyond the P_2' site for non-hydrogen bonding, lipophilic moieties is observed. We next evaluated the steric and the electronic environment of the allylic moiety. For example, comparison of acetate **45** to benzoate **52**, trifluoroacetate **53**, and allyl ether **55** demonstrates a pronounced steric (Table V) requirement for good inhibitory activity; however, the enhanced hydrophobicity of the trifluoroacetate moiety (**53**) relative to the acetate moiety (**45**) has little effect on inhibitory activity.

The branched chain substituents (compounds **49–51**, Table V) are intriguing, since they introduce a new level of lipophilicity as well as a newly formed chiral center. Since there are clear steric constraints imposed by the binding protein on this segment of the inhibitor, we expected the absolute configuration of the newly formed center to play a critical role in the inhibitory activity. Unfortunately, the diastereoselectivity is quite low (~65:35) and separation of the resulting diastereomers proved impractical. Nevertheless, diastereomeric compounds **49–51**, which were prepared via nickel-catalyzed 1,4-addition of the vinyl zirconium reagent to the corresponding Michael acceptors, demonstrated interesting activity (Table V). For example, when the Y-terminus (Table V) was either an acyclic or a cyclic ketone (**49** and **50**, respectively), moderate binding to FKBP was observed (~10 μM), whereas lactone **51** was a relatively poor inhibitor (42 μM). Finally, when the sp^2-hybridized linker moiety is a highly polarized ketone (compound **56**, Table V), the inhibitory activity is reduced relative to the corresponding trans olefinic linker.

Thus, by following relatively straightforward design elements we have effectively designed micromolar and submicromolar peptide-like FKBP inhibitors, which span the P_1 through P_4' sites. The most surprising and the most enlightening aspects of these molecules are the apparent requirements of hydrophobic residues along the entire P_1 through P_4' network and the pronounced steric constraints of the P_2' through P_4' subsites (see Figure 2). It is chiefly these observations that guided the design of non-peptide inhibitors, which ultimately resulted in the successful implementation of a trans double bond spanning the P_3'–P_4' region. It is hoped that structural investigations of these novel, high-affinity ligands bound to FKBP will provide new opportunities for further refinement of their binding interactions.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Bruker (^{1}H NMR, 250 MHz, 300 MHz; ^{13}C NMR, 62.8 MHz, 75 MHz) spectrometer. The carbon type (methine, methylene, methyl, or quaternary) was determined by DEPT experiments. High-

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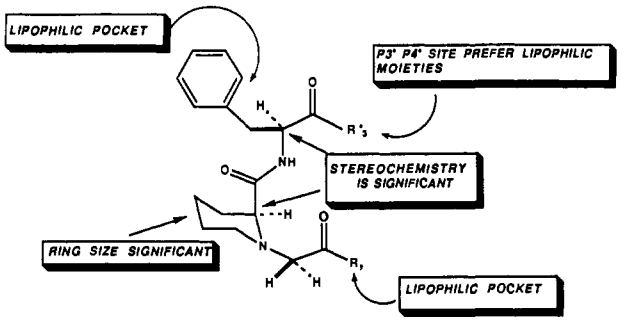

Figure 2. Summary of the structural requirements of the synthetic FKBP inhibitors.

resolution mass spectra were recorded on either a Kratos profile or a Kratos concept I-S.

General Procedure for the Preparation of Amido Ketones. Preparation of 2-Thienyl Homoallylic Alcohol. A 1-L three-neck flask fitted with an N_2 inlet, a stoppered addition funnel, and a thermometer was flame-dried under N_2 and charged with (*S*)-(−)-(3-hydroxy-2-methylpropyl) triphenylphosphonium bromide (50.0 g, 120 mmol) (Aldrich) and 250 mL anhydrous THF. The stirred mixture was allowed to cool to 0 °C in an ice bath, and phenyllithium (120 mL of a 2.0 M solution) was then added. An orange solution formed. The ice bath was removed at the end of the addition, and stirring was continued for an additional 2 h. A solution of 2-thiophenecarboxaldehyde (13.5 g, 120 mmol) in THF (100 mL) was added dropwise over 1 h. White precipitates formed, and the resulting mixture was allowed to stir at room temperature overnight. TLC [silica, ethyl acetate–hexane (10:90)] showed no aldehyde and one new spot less polar than the aldehyde (R_f ~ 0.2; UV positive). Water (100 mL) and diethyl ether (100 mL) were added and the layers separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting amber oil was flash chromatographed on silica using ethyl acetate–hexane (15:85) affording 18.5 g (92%) of the homoallylic alcohol as a light amber oil: ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3 H), 2.22 (br t, 1 H), 2.46 (hept, 1 H), 3.45–3.60 (br m, 2 H), 3.93 (dd, 1 H), 6.57 (d, 1 H), 6.88–6.96 (m, 1 H), 7.09 (d, 1 H); ^{13}C NMR δ 142.6, 132.4, 127.3, 128.0, 124.0, 123.6, 67.3, 39.9, 16.4.

2-Thienyl Homoallylic Silyl Ether. To a stirred solution of the homoallylic alcohol from above (5.05 g, 30.0 mmol) in CH_2Cl_2 (50 mL) under N_2 was added *tert*-butyldimethylsilyl chloride (4.75 g, 31.5 mmol), followed by imidazole. A flocculent precipitate formed. After 30 min TLC [silica, ethyl acetate–hexane (10:90)] showed no starting material and one new less polar material (R_f ~ 0.9, UV positive). The reaction was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting pale amber oil was flashed chromatographed on silica using hexane to afford 8.12 (96%) of the silyl ether as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.91 (s, 9 H), 1.10 (d, 3 H), 3.47–3.62 (m, 2 H), 6.02 (dd, 1 H), 6.55 (d, 1 H), 6.87–6.97 (m, 2 H), 7.10 (d, 1 H); ^{13}C NMR δ 143.2, 133.3, 127.2, 124.4, 123.2, 122.7, 67.9, 39.6, 25.9, 19.4, 16.4.

Preparation of Methyl Prolyl Oxalate *tert*-Butyl Ester. A solution of methyl oxalyl chloride (18.8 g, 153 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a CH_2Cl_2 (250 mL) solution of L-proline-*tert*-butyl ester (25.0 g, 146 mmol) and triethylamine (16.3 g, 161 mmol) maintained at 0 °C under N_2. After 30 min, TLC [silica, ethyl acetate–hexane (25:75)] showed one new less polar material. The solids were filtered, and the filtrate was washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording 36.0 g (96%) of the oxamate as a pale yellow oil. NMR spectra were acquired on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) δ 1.34, 1.35 (2 s, 9 H), 1.73–2.28 (m, 4 H), 3.46–3.72 (m, 2 H), 3.71, 3.75 (2 s, 3 H), 4.30, 4.66 (2 dd, 1 H); ^{13}C NMR δ 170.8, 170.0, 161.9, 161.7, 157.9, 157.8, 82.1, 81.7, 61.0, 60.0, 52.7, 52.6, 48.0, 47.6, 31.4, 28.5, 27.81, 27.76, 24.6, 22.1.

Preparation of Amido Ketone 1. A solution of the 2-thienyl homoallylic silyl ether (6.57, 23.2 mmol) in THF (100 mL) under N_2 was allowed to cool to −30 to −40 °C via a dry ice–acetone bath. A hexane solution of *n*-butyllithium (15.5 mL of a 1.5 M solution in hexanes, 23.2 mmol) was added dropwise over 10 min. The dark solution was maintained at −30 to −40 °C for 2 h and then allowed to cool to −78 °C. A solution of the methyl prolyl oxamate in THF (20 mL) was added dropwise rapidly, causing the temperature to rise to −50 °C. After 1 h, TLC [silica, ethyl acetate–hexane (25:75)] showed a pair of new spots (R_f ~0.4, UV, $KMnO_4$ stain). A 1:1 mixture of water and diethyl ether (200 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording 13.0 g of an amber oil. This oil was flash chromatographed on 600 g silica using ethyl acetate–hexane (15:85) as eluent affording 8.47 g (72%) compound 1 as a pale yellow oil. NMR spectra were acquired on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) 0.01 (s, 6 H), 0.83 (s, 9 H), 1.29, 1.47 (2 s, 9 H), 1.80–2.54 (m, 5 H), 3.49 (dd, 2 H), 3.57–3.80 (m, 2 H), 4.43, 4.73 (2 dd, 1 H), 6.21, 6.28 (2 dd, 1 H), 6.47, 6.52 (2 d, 1 H), 6.88 (dd, 1 H), 7.85 (dd, 1 H); ^{13}C NMR δ 182.5, 180.9, 171.0, 170.5, 163.6, 162.9, 154.3, 154.1, 139.0, 138.5, 138.2, 137.8, 137.0, 136.7, 125.8, 125.4, 122.5, 122.4, 82.0, 81.7, 60.4, 59.6, 47.6, 47.3, 39.9, 39.8, 31.6, 29.0, 27.9, 27.7, 25.8, 24.7, 22.2, 18.2, 16.0, 15.9, 14.2; HREI calcd for $C_{26}H_{41}NO_5SSi$ $(M)^+$ 507.2475, found 507.2488.

Preparation of Amido Ketone 2. Tetrabutylammonium fluoride (16.0 mL of a 1.0 M solution in THF, 16.0 mmol) was added to a stirred THF solution (100 mL) of compound 1 (7.97 g, 15.7 mmol) at room temperature under N_2. After 30 min, TLC [silica, ethyl acetate–hexane (25:75)] showed no remaining 1 and one more polar material (R_f ~ 0.05, UV, $KMnO_4$ positive). The reaction mixture was poured onto H_2O–Et_2O (1:1, 200 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording 8.90 g of an amber oil. This oil was flash chromatographed on 350 g silica using ethyl acetate–hexane (50:50) as eluent affording 4.79 g (78%) of compound 2 as a viscous yellow oil. NMR spectra were acquired on a mixture of rotamers: ^{1}H NMR δ 1.06 (dd, 3 H), 1.31, 1.49 (2 s, 9 H), 1.83–2.34 (m, 4 H), 2.45–2.58 (m, 1 H), 3.47–3.80 (m, 4 H), 4.46, 4.76 (2 dd, 1 H), 6.20, 6.27 (2 dd, 1 H), 6.52, 6.58 (2 d, 1 H), 6.92, 6.94 (2 d, 1 H), 7.84, 7.89 (2 d, 1 H); ^{13}C NMR δ 182.2, 180.8, 171.0, 170.5, 163.6, 162.8, 153.8, 153.7, 138.2, 137.7, 126.1, 125.7, 123.3, 123.2, 82.1, 81.8, 66.9, 60.5, 59.7, 47.7, 47.4, 40.0, 31.6, 29.0, 28.0, 27.8, 24.8, 22.2, 16.0; HREI calcd for $C_{20}H_{22}NO_5S$ $(M)^+$ 393.1602, found 393.1611.

Preparation of Amido Ketone 3. A Et_2O solution (15 mL) of the 2-thienyl homoallylic silyl ether (1.68 g, 5.96 mmol) was allowed to cool to −78 °C followed by dropwise addition of *tert*-butyllithium (3.5 mL of a 1.7 M solution in pentane, 5.96 mmol). After 1 h, a solution of the methyl oxamate of prolylphenylalanine *tert*-butyl ester in 10 mL of THF was added dropwise. After 1 h, TLC [silica, ethyl acetate–hexane (40:60)] indicated no remaining starting materials and a new pair of more polar materials (R_f ~0.3, UV positive). The reaction was quenched with H_2O (15 mL), and layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording a viscous oil. This oil was flash chromatographed on 100 g of silica using ethyl acetate–hexane (20:80) followed by ethyl acetate–hexane (35:65) as eluent affording 690 mg (18%) of compound 3 as a viscous yellow oil. NMR spectra were obtained on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) δ 0.01–2.02 (2 s, 6 H), 0.83, 0.87 (2 s, 9 H), 1.05, 1.07 (2 d, 3 H), 1.33, 1.40 (2 d, 9 H), 1.55–2.60 (m, 5 H), 2.86–3.20 (m, 2 H), 3.45–3.71 (m, 4 H), 4.58–4.77 (m, 2 H), 6.20–6.48 (m, 1 H), 6.48, 6.51 (2 d, 1 H), 6.89, 6.97 (2 d, 1 H), 7.08–7.30 (m, 5 H), 7.83, 7.88 (d, 1 H); ^{13}C NMR δ 181.8 (Q), 180.9 (Q), 171.9 (Q), 170.4 (Q), 170.2 (Q), 170.1 (Q), 169.8 (Q), 164.4 (Q), 163.4 (Q), 154.2 (Q), 139.2 (CH), 138.8 (CH), 138.2 (CH), 138.1 (CH), 136.8 (Q), 136.1 (Q), 136.0 (Q), 129.6 (CH), 129.5 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 126.9 (CH), 126.8 (CH), 125.8 (CH), 125.6 (CH), 122.4 (CH), 82.4 (Q), 82.3 (Q), 67.4 (CH_2), 62.9 (Q), 61.2 (CH), 60.4 (CH_2), 60.2 (CH), 59.9 (Q), 53.9 (CH), 53.5 (CH), 51.7 (Q), 47.9 (CH_2), 47.1 (CH_2), 39.9 (CH), 38.0 (CH_2), 37.99 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 29.1 (U), 28.0 (CH_3), 27.9 (CH_3), 27.7 (CH_2),

26.8 (CH_3), 25.9 (CH_3), 24.9 (CH_2), 22.1 (CH_2), 21.0 (CH_2), 18.3 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 14.2 (CH_3).

Preparation of Amido Ketone 4. Compound **4** was prepared from compound **3** by the procedure used to prepare compound 2. NMR spectra were obtained on a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 1.07, 1.09 (2 d, 3 H), 1.32, 1.40 (2 s, 9 H), 1.78–2.32 (m, 4 H), 2.43–2.61 (m, 1 H), 2.87–3.20 (m, 2 H), 3.44–3.73 (m, 4 H), 4.57–4.78 (m, 2 H), 6.14–6.38 (m, 1 H), 6.53, 6.59 (2 d, 1 H), 6.92, 6.97 (2 d, 2 H), 7.11–7.32 (m, 5 H), 7.74, 7.89 (2 d, 1 H).

General Procedure for the Preparation of Amino Ketones. Preparation of Amino Ketone 5. (*R*)-Ethyl 5-[1-(*tert*-Butyldimethylsilyloxy)-2-methyl-3-buten-4-yl]-2-thiophenecarboxylate. To a stirred THF solution (10 mL) of the 2-thienyl homoallylic silyl ether from above (1.02 g, 3.61 mmol) maintained at −30 °C to −40 °C in a dry ice–acetone bath was added *n*-butyllithium (2.7 mL of a 1.5 M solution in hexanes, 4.0 mmol). After 1 h at −30 °C, the solution was allowed to cool to −78 °C and cannulated into a −78 °C THF solution (5 mL) of ethyl chloroformate (434 mg, 4.00 mmol). After 10 min, the reaction was poured onto saturated NH_4Cl–H_2O (1:1, 20 mL) and Et_2O (10 mL). The layers were separated, and the organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording an amber oil. This oil was flash chromatographed on 75 g of silica using ethyl acetate–hexane (2:98) as eluent to afford 1.06 g (83%) of the ester as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.89 (s, 9 H), 1.07 (d, 3 H), 1.37 (t, 3 H), 2.48 (hept, 1 H), 3.52 (dd, 2 H), 4.33 (q, 2 H), 6.18 (dd, 1 H), 6.49 (d, 1 H), 6.85 (d, 1 H), 7.61 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.3, 149.8, 136.7, 133.7, 130.8, 124.8, 122.5, 87.6, 61.0, 39.7, 26.0, 18.3, 16.1, 14.4; HRFAB calcd for $C_{35}H_{52}N_2O_5SSi$ $(M)^+$ 640.3364, found $(M + H)^+$ 641.3471.

(*R*)-5-(α-Bromoacetyl)-2-[1-(*tert*-butyldimethylsilyloxy)-2-methyl-3-buten-4-yl]thiophene. The bromomethyl ketones were prepared according to the known procedure.[26] For example, to a THF solution (3 mL) of diisopropylamine (243 mg, 2.40 mmol) maintained at 0 °C under N_2 was added *n*-butyllithium (1.5 mL of a 1.5 M solution in hexanes, 2.20 mmol). This solution was added dropwise via a syringe to a THF solution (3 mL) of dibromomethane (382 mg, 2.20 mmol) maintained at −78 °C under N_2. After 5 min, a THF solution (2 mL) of the thiophene ethyl ester (355 mg, 1.00 mmol) prepared above was added dropwise. After 10 min, 1.0 mL of a hexane solution of *n*-butyllithium (1.5 M, 1.5 mmol) was added in a dropwise fashion. After 5 min, the resulting mixture was cannulated into a −78 °C solution of acetyl chloride (1.5 mL, 20 mmol) in ethanol (10 mL). After 1 min, the reaction was poured onto a mixture (2:1, 150 mL) of Et_2O and dilute $NaHCO_3$. Layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organics were washed with 1 N HCl (2 × 50 mL) and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording 460 mg of an amber oil. This oil was flash chromatographed on 50 g of silica using ethyl acetate–hexane (5:95) as eluent to afford 236 mg (58%) of the bromomethyl ketone as an amber oil: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.08 (d, 3 H), 2.50 (hept, 1 H), 3.53 (d, 2 H), 4.30 (s, 2 H), 6.27 (dd, 1 H), 6.52 (d, 1 H), 6.91 (d, 1 H), 7.63 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 184.0, 153.1, 138.8, 137.7, 134.3, 125.4, 122.2, 67.4, 39.5 (CH_2Br), 30.3, 25.9, 18.3, 16.0.

Amino Ketone 5. Potassium fluoride on Celite (50% by weight, 300 mg) was added to a stirred acetonitrile (5 mL) solution of the (bromoacetyl)thiophene derivative from above (154 mg, 0.382 mmol) and prolylphenylalanine *tert*-butyl ester (122 mg, 0.382 mmol) under N_2. The mixture was stirred at room temperature overnight. TLC [silica, CH_2Cl_2–CH_3OH–NH_4OH (90:10:.1)] indicated no remaining dipeptide. TLC [ethyl acetate–hexane (25:75)] indicated no bromide and one new more polar material (R_f ~0.1, UV positive). The solids were filtered, and the filtrate was concentrated in vacuo affording an amber oil. This oil was flash chromatographed on 40 g silica using acetate–hexane (1:1) to afford 149 mg (66%) of the amino ketone as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.86 (s, 9 H), 1.05 (d, 3 H), 1.35 (s, 9 H), 1.42–1.82 (m, 4 H), 2.08–2.24 (m, 1 H), 2.41–2.62 (m, 2 H), 2.98 (dd, 1 H), 3.09–3.20 (m, 2 H), 3.36 (dd, 1 H), 3.52 (d, 2 H), 3.82–4.08 (q, 2 H, NCH_2CO), 4.61–4.71 (m, 1 H), 6.22 (dd, 1 H), 6.48 (d, 1 H), 6.84 (d, 1 H), 7.12–7.28 (m, 5 H), 7.52 (d, 1 H), 7.95 (d, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 189.6 ($COCH_2Br$), 174.3, 170.6, 151.4, 139.3, 139.0, 136.7, 132.6, 129.3, 128.3, 126.8, 125.2, 122.4, 81.8, 67.5, 66.8, 59.3, 53.7, 53.3, 39.8, 38.0, 30.8, 27.9, 25.9, 24.7, 18.3, 16.0.

Amino Ketone 6. L-Prolyl-L-phenylalanine *tert*-butyl ester was alkylated with α-bromo-*m*-methoxyacetophenone using the same procedure as for the preparation of compound **5**: ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9 H), 1.45–1.80 (m, 3 H), 2.09–2.28 (m, 1 H), 2.49–2.59 (m, 1 H), 2.96 (dd), 3.10–3.21 (m, 2 H), 3.36 (dd, 1 H), 3.80 (s, 3 H), 4.08 (AB quartet, 2 H), 4.59–4.69 (m, 1 H), 7.04–7.46 (m, 9 H), 7.96 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.5 (Q), 170.7 (Q), 160.0 (Q), 137.3 (Q), 136.8 (Q), 129.8 (CH), 129.4 (CH), 129.2 (U), 128.4 (CH), 126.9 (CH), 120.5 (CH), 119.9 (CH), 112.1 (CH), 81.8 (Q), 66.9 (CH), 59.7 (CH_2), 55.5 (CH_3), 53.5 (CH_2), 53.4 (CH), 38.1 (CH_2), 30.9 (CH_2), 28.0 (CH_3), 24.9 (CH_2).

Preparation of Amino Ketone 7. *cis*-3-Methoxycyclohexyl α-Bromomethyl Ketone. The bromomethyl ketone was prepared from *cis*-3-methoxycyclohexanecarboxylic acid ethyl ester following the same procedure used to prepare the bromomethyl thienyl ketone above: ^{1}H NMR ($CDCl_3$) δ 1.03–1.39 (m, 4 H), 1.75–1.92 (m, 2 H), 1.99 (br d, 1 H), 2.19 (br d, 1 H), 2.64–2.79 (m, 1 H), 3.09–3.22 (m, 1 H), 3.29 (s, 3 H), 3.95 (s, 2 H); ^{13}C NMR δ 203.2 (Q), 78.3 (CH), 55.7 (CH_3), 46.2 (CH), 33.7 (CH_2), 33.1 (CH_2), 31.2 (CH_2), 27.9 (CH_2), 23.2 (CH_2).

L-Prolyl-L-phenylalanine *tert*-butyl ester was alkylated with the cyclohexyl bromomethyl ketone from above using the same conditions to prepare **5** to afford the compound **7** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.03–1.30 (m, 4 H), 1.39 (s, 9 H), 1.43–2.20 (m, 8 H), 2.28–2.46 (m, 2 H), 2.95 (dd, 1 H), 3.05–3.24 (m, 4 H), 3.31 (s, 3 H), 3.53 (AB quartet, 2 H), 4.62–4.72 (m, 1 H), 7.12–7.28 (m, 5 H), 7.81–7.88 (m, 1 H); ^{13}C NMR δ 209.6, 174.3, 170.6, 136.6, 129.3, 128.3, 126.8, 81.8, 78.6 ($CHOCH_3$), 66.8, 61.2, 55.6, 53.6, 53.0, 46.9, 38.0, 33.5, 33.3, 31.5, 31.4, 30.6, 27.9, 27.6, 24.7, 23.6, 23.5: HREI calcd for $C_{27}H_{40}N_2O_5$ $(M)^+$ 472.2927, found 472.2959.

Amino Ketone 8. L-Prolyl-L-phenylalanine *tert*-butyl ester was alkylated with *N*-(*tert*-butyloxycarbonyl)hexahydropheny lalanine bromomethyl ketone using the same conditions as in the preparation of **5** to afford compound **8** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.70–2.16 (m, 34 H), 2.33–2.47 (m, 1 H), 2.93 (dd, 1 H), 3.01–3.21 (m, 2 H), 3.56 (AB quartet, 2 H), 4.22–4.37 (m, 1 H), 4.61–4.72 (m, 1 H), 5.16 (d, 1 H), 7.10–7.28 (m, 5 H), 7.83 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 208.3 (Q), 174.2 (Q), 170.9 (Q), 155.5 (Q), 136.7 (Q), 129.2 (CH), 128.2 (CH), 126.7 (CH), 81.8 (Q), 79.7 (Q), 67.1 (CH), 60.3 (CH_2), 55.4 (CH), 53.7 (CH_2), 53.0 (CH), 39.0 (CH_2), 37.9 (CH_2), 34.1 (CH), 33.9 (CH_2), 32.3 (CH_2), 30.6 (CH_2), 28.3 (CH_3), 27.9 (CH_3), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 24.6 (CH_2).

Amido Ketone 9. L-Pipecolinyl-L-phenylalanine *tert*-butyl ester was converted to its methyl oxamate according to the procedure previously described for the prolyl analog in the preparation of compound **1**. The yield of the oxamate was 88% as a yellow oil. NMR spectra were obtained on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) δ 1.25–1.70 (m, 13 H), 2.05–2.32 (m, 2 H), 2.68–2.80 (m, 1 H), 2.89–3.23 (m, 2 H), 3.28–3.36 (m, 1 H), 3.73–3.88 (m, 5 H), 4.12–4.25 (m, 1 H), 4.64–4.79 (m, 1 H), 5.00–5.05 (m, 1 H), 6.31, 6.77 (2 d, 1 H), 7.06, 7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 168.7, 168.1, 162.8, 161.6, 160.6, 136.2, 136.1, 129.4, 129.3, 128.5, 128.4, 127.0, 126.9, 82.4, 57.2, 53.6, 53.0, 52.7, 51.8, 44.3, 39.2, 38.1., 38.0, 27.9, 27.8, 26.4, 25.2, 25.1, 24.3, 20.3, 20.2.

This oxamate was treated with lithiated thiophene homoallylic silyl ether as previously described in the preparation of compound 1 to afford the pipecolinyl analog of compound 1 (24% yield). NMR spectra were acquired on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.87 (s, 9 H), 1.06 (2 d, 3 H), 1.28–1.72 (m, 14 H), 2.02–2.33 (m, 1 H), 2.43–2.57 (m, 1 H), 2.78–3.36 (m, 3 H), 3.42–3.56 (m, 2 H), 4.22–4.37 (m, 1 H), 4.66–4.77 (m, 1 H), 5.18 (br d, 0.5 H), 6.28, 6.34 (2 d, 1 H), 6.42 (br d, 0.5 H), 6.50, 6.55 (2 d, 1 H), 6.91 (d, 1 H), 7.08–7.30 (m, 5 H), 7.66, 7.68 (2 d, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.3, 183.0, 170.3, 169.0, 168.4, 166.4, 165.1, 155.2, 154.4, 139.5, 139.4, 137.9, 137.5, 137.1, 136.3, 136.1, 129.5, 129.4, 128.5, 128.4, 126.9, 126.9, 125.9, 122.3, 122.2, 82.5,

(26) Kowalski, C. J.; Hague, S. M. Bromomethyl Ketones and Enolates: Alternative Products from Ester Homologation Reactions. *J. Org. Chem.* **1985**, *50*, 5140–5142.

82.3, 67.4, 56.8, 53.8, 53.7, 52.1, 44.4, 39.8, 39.3, 38.1, 37.9, 28.0, 26.6, 25.9, 25.7, 25.1, 24.9, 20.4, 18.3, 16.0.

The silyl protecting group was removed using the conditions previously described for the preparation of compound 2 from compound 1 to afford 9 in 61% yield as a yellow oil. NMR spectra were obtained on a mixture of rotamers: ^{1}H NMR ($CDCl_3$) δ 1.05–1.13 (m, 3 H), 1.30–1.72 (m, 14 H), 2.12–2.33 (m, 2 H), 2.46–2.61 (m, 1 H), 2.78–3.26 (m, 2 H), 3.38–3.62 (m, 3 H), 4.23–4.39 (m, 1 H), 4.66–4.80 (m, 1 H), 5.13–5.21 (m, 2 H), 6.26, 6.32 (2 dd, 1 H), 6.50–6.63 (m, 2 H), 6.96 (d, 1 H), 7.08–7.30 (m, 5 H), 7.66, 7.69 (2 d, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.2, 182.9, 170.3, 170.2, 169.0, 168.4, 166.3, 165.1, 154.7, 154.0, 139.0, 138.8, 137.8, 137.5, 137.1, 136.8, 136.2, 136.1, 129.4, 129.3, 128.4, 128.3, 126.9, 126.2, 126.1, 123.0, 122.9, 82.5, 82.4, 66.8, 60.3, 56.8, 53.8, 53.7, 52.1, 44.3, 39.9, 39.2, 38.0, 37.7, 27.8, 26.6, 25.7, 25.1, 24.8, 21.0, 20.3, 16.0, 14.1; HREI calcd for $C_{30}H_{35}N_2O_6S$ $(M)^+$ 554.2240, found 554.2433.

General Procedure A. *N*-CBZ-*tert*-Pipecolinyl-L-phenylalanyl *tert*-Butyl Ester. To a CH_2Cl_2 solution (25 mL) of *N*-CBZ-L-pipecolinic acid (2.63 g, 10.0 mmol), L-phenylalanine *tert*-butyl ester (2.21 g, 10.0 mmol), and 1-hydroxybenzotriazole monohydrate (1.42 g, 10.5 mmol) maintained at 0 °C under N_2 was added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.01 g, 10.5 mmol). The reaction was stirred at 0 °C for 1 h and then at room temperature for 1 h. TLC [ethyl acetate–hexane (25:75)] indicated no remaining phenylalanine *tert*-butyl ester and one new material ($R_f \sim 0.4$, UV). The reaction was concentrated in vacuo and the resulting residue partitioned between water and ethyl acetate (1:1, 100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed with 5% citric acid (25 mL), dilute aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo affording 4.48 g (96%) of the dipeptide as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25–1.65 (m, 15 H), 2.18–2.64 (m, 2 H), 2.89–3.08 (m, 1 H), 3.17, 3.22 (2 d, 1 H), 3.82, 4.12 (m, 1 H), 4.68–4.88 (m, 2 H), 5.14 (s, 2 H), 6.47 (br d, 1 H), 7.07–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.9, 136.2, 129.3, 128.5, 128.3, 128.0, 127.9, 126.9, 82.3, 67.6, 54.5, 53.4, 41.8, 37.9, 27.9, 25.6, 24.5, 20.2.

General Procedure B. L-Pipecolyl-L-phenylalanine *tert*-Butyl Ester. The carbobenzyloxy group of *N*-CBZ-L-pipecolinyl-L-phenylalanine methyl ester was removed using standard catalytic hydrogenolysis conditions of either (a) 10% palladium hydroxide in ethanol at 40 psi on a Parr shaker or (b) phase-transfer hydrogenolysis with 10% palladium hydroxide in ethanol using ammonium formate as a hydrogen source: ^{1}H NMR ($CDCl_3$) δ 1.27–1.90 (m, 14 H), 1.54–2.70 (m, 3 H), 2.88–3.23 (m, 4 H), 4.67–4.76 (m, 1 H), 7.12–7.31 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 170.8, 136.4, 129.5, 128.3, 126.8, 82.1, 59.9, 53.0, 45.4, 38.1, 29.8, 27.9, 25.6, 23.8.

General Procedure C. Preparation of Amino Ketone 10. To a stirred solution of L-pipecolyl-L-phenylalanine *tert*-butyl ester (589 mg, 1.77 mmol) and 2-bromo-3′-methoxyacetophenone (447 mg, 1.95 mmol) in acetonitrile (20 mL) at room temperature N_2 was added potassium fluoride (50% by weight on Celite, 1 g). The mixture was stirred overnight. TLC [silica, CH_2Cl_2–MeOH–NH_4OH (90:10:.5)] indicated no remaining pipecolylphenylalanine *tert*-butyl ester. TLC [silica, ethyl acetate–hexane (25:75)] indicated one new, more polar material ($R_f \sim 0.2$, UV). The reaction was diluted with CH_2Cl_2, the solids were filtered, and the filtrate was concentrated in vacuo affording a viscous oil. The oil was flash chromatographed on 35 g silica using ethyl acetate–hexane (25:75) as eluent to afford 715 mg (84%) of compound 10 as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.20–1.84 (m, 15 H), 2.13 (dt, 1 H), 2.88–2.99 (m, 3 H), 3.11 (dd, 1 H), 3.82 (s, 3 H), 3.89 (AB quartet, 2 H), 4.59–4.68 (m, 1 H), 7.03–7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 196.9 (Q), 173.9 (Q), 170.5 (Q), 159.7 (Q), 137.6 (Q), 136.6 (Q), 129.4 (CH), 129.2 (CH), 128.3 (CH), 126.7 (CH), 120.4 (CH), 119.6 (CH), 112.0 (CH), 81.7 (Q), 66.6 (CH), 62.3 (CH_2), 55.3 (CH_3), 53.2 (CH), 52.7 (CH_2), 37.8 (CH_2), 29.8 (CH_2), 27.7 (CH_3), 24.6 (CH_2), 23.0 (CH_2); HREI calcd for $C_{28}H_{36}N_2O_5$ $(M)^+$ 480.2615, found 480.2627.

***N*-BOC-L-Pipecolyl-L-*p*-nitrophenylalanine *tert*-Butyl Ester.** General procedure A was used to couple *N*-BOC-L-pipecolinic acid[27] and *p*-nitrophenylalanine *tert*-butyl ester to afford the dipeptide (95% yield) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.25–1.67 (m, 23 H), 2.12–2.68 (br m, 2 H), 3.06–3.32 (m, 2 H), 3.79–4.12 (br m, 1 H), 4.58–4.83 (br m, 1 H), 6.46–6.69 (br m, 1 H), 7.73 (AA′BB′ quartet, 4 H); ^{13}C NMR ($CDCl_3$) 171.1, 169.7, 147.0, 144.4, 130.4, 123.5, 83.0, 80.8 (br), 53.3, 38.1, 28.2, 27.9, 25.4, 24.7, 20.4.

General Procedure D. L-Pipecolyl-L-*p*-nitrophenylalanine *tert*-Butyl Ester. To a stirred ethyl acetate (10 mL) solution of *N*-BOC-L-pipecolyl-L-*p*-nitrophenylalanine *tert*-butyl ester (694 mg, 1.45 mmol) at room temperature was added a saturated solution of gaseous HCl in ethyl acetate (5 mL) under N_2. After 3 h, TLC [ethyl acetate–hexane (25:75)] indicated no remaining starting material. The reaction was concentrated in vacuo and the resulting residue partitioned between CH_2Cl_2 and dilute $NaHCO_3$ solution. The CH_2Cl_2 layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 376 mg (69%) of the dipeptide as a yellow foam: ^{1}H NMR ($CDCl_3$) δ 1.27–2.21 (m, 15 H), 3.09–3.45 (m, 4 H), 4.12–4.24 (m, 1 H), 4.62–4.72 (m, 1 H), 7.87 (AA′BB′ quartet, 4 H), 8.18 (d, 1 H); ^{13}C NMR ($CDCl_3$) 169.3, 168.7, 146.9, 144.3, 130.6, 123.5, 82.9, 57.2, 54.1, 43.5, 37.0, 27.9, 27.3, 21.7, 21.6.

The above procedures were used to prepare compounds 11–35.

Compound 12. The yield of 12 was 78% as an oil: ^{1}H NMR ($CDCl_3$) δ 1.04–2.36 (m, 16 H), 3.0–3.14 (m, 2 H), 3.73–4.06 (m, 5 H), 4.41–4.52 (m, 1 H), 4.62 (heptet, 1 H), 6.94–7.71 (m, 10 H); ^{13}C NMR ($CDCl_3$) 174.2, 171.4, 159.8, 140.7, 137.4, 129.7, 128.4, 128.3, 126.1, 120.4, 119.9, 68.8, 66.5, 62.6, 55.4, 53.0, 51.8, 33.7, 31.9, 29.1, 24.6, 23.1, 21.6; HREI calcd for $C_{28}H_{36}N_2O_5$ $(M)^+$ 480.2615, found 480.2621.

Compound 14. The yield of 14 was 65% as a viscous colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.74–2.37 (m, 29 H), 2.98–3.13 (m, 2 H), 3.74–4.20 (m, 5 H), 4.31–4.43 (m, 1 H), 4.92 (heptet, 1 H), 7.06–7.13 (m, 1 H), 7.30–7.55 (m, 4 H); HREI calcd for $C_{28}H_{42}N_2O_5$ $(M)^+$ 486.3083, found 486.3099.

Compound 17. The yield of 17 was 57% as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.22–2.23 (m, 15 H), 2.91–3.27 (m, 4 H), 3.70–4.05 (m, 6 H), 4.61–4.70 (m, 1 H), 7.08 (dd, 1 H), 7.24–7.60 (m, 6 H), 8.07 (d, 2 H); ^{13}C NMR ($CDCl_3$) 196.9, 174.2, 169.8, 159.8, 144.7, 130.1, 129.5, 123.5, 120.3, 119.7, 112.1, 82.3, 66.4, 62.2, 55.4, 52.9, 52.8, 37.5, 29.8, 27.8, 24.6, 23.0; HREI calcd for $C_{28}H_{35}N_3O_7$ $(M)^+$ 525.2466, found 525.2475.

Compound 20. The yield of 20 was 78% as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.18–1.78 (m, 14 H), 2.13–2.23 (br m, 1 H), 2.63–2.75 (br m, 1 H), 2.01, 3.00 (m, 5 H), 3.18 (dd, 1 H), 3.84–3.90 (m, 5 H), 4.51–4.62 (m, 2 H), 6.66 (d, 1 H), 7.03–7.36 (m, 12 H), 7.41–7.48 (m, 2 H), 7.73 (d, 1 H); ^{13}C NMR ($CDCl_3$) 197.5, 174.2, 170.5, 170.1, 159.8, 137.4, 137.0, 136.3, 129.6, 129.5, 129.2, 128.5, 128.3, 128.2, 126.8, 126.7, 120.6, 119.7, 112.5, 82.0, 65.5, 62.0, 55.4, 54.4, 53.6, 52.3, 38.1, 37.6, 28.1, 27.8, 24.1, 22.6; HREI calcd for $C_{37}H_{45}N_3O_6$ $(M)^+$ 627.3297, found $(M + H)^+$ 628.3385.

Compound 21. The yield of 21 was 85% as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.72 (d, 6 H), 1.32 (s, 9 H), 1.33–1.78 (m, 6 H), 1.92–2.06 (m, 1 H), 2.11–2.28 (m, 1 H), 2.69–3.01 (m, 3 H), 3.26 (dd, 1 H), 3.28–3.92 (m, 5 H), 4.25 (dd, 1 H), 4.56–4.66 (m, 1 H), 6.69 (br d, 1 H), 7.03–7.49 (m, 9 H), 7.78 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 197.1, 174.4, 170.9, 170.4, 159.8, 137.0, 129.5, 129.2, 128.5, 126.7, 120.6, 119.9, 112.3, 81.7, 65.5, 62.1, 57.3, 55.4, 54.7, 52.4, 37.7, 31.4, 28.3, 27.9, 24.2, 22.5, 18.7, 17.5; HREI calcd for $C_{33}H_{45}N_3O_6$ $(M)^+$ 579.3297, found 579.3278.

Compound 23. The yield of 23 was 43% as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.69 (d, 3 H), 0.79 (t, 3 H), 0.85–1.77 (m, 16 H), 2.13–2.26 (br m, 1 H), 2.91–3.04 (m, 2 H), 3.27 (dd, 1 H), 3.78–3.99 (m, 5 H), 4.32 (dd, 1 H), 4.55–4.68 (m, 1 H), 6.70 (br d, 1 H), 7.06–7.52 (m, 9 H), 7.81 (br d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.1, 174.4, 170.6, 170.3, 159.7, 137.3, 136.9, 129.5, 129.2, 128.5, 126.7, 120.5, 119.8, 112.2, 81.7, 65.5, 62.1, 56.5, 55.3, 54.6, 52.3, 38.0, 37.6, 28.4, 27.9, 25.1, 24.2, 22.6, 15.0, 11.6; HRFAB calcd for $C_{34}H_{47}N_3O_6$ $(M)^+$ 593.3453, found $(M + H)^+$ 594.3560.

Compound 25. The yield of compound 25 was 70% as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.04–1.83 (m, 12 H), 2.11–2.45 (m,

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2 H), 2.63–2.75 (m, 1 H), 2.89–3.12 (m, 3 H), 3.23 (dd, 1 H), 3.72–3.92 (m, 5 H), 4.45–4.66 (m, 2 H), 4.95–5.39 (m, 5 H), 6.82 (d, 1 H), 7.06–7.47 (m, 19 H); ^{13}C NMR ($CDCl_3$) 197.8, 174.5, 171.6, 171.0, 159.8, 156.7, 137.3, 136.9, 135.1, 129.7, 129.2, 128.6, 128.5, 128.4, 128.3, 128.0, 126.8, 120.5, 119.7, 112.6, 67.0, 66.5, 65.1, 61.9, 59.1, 55.4, 54.6, 52.2, 51.9, 40.5, 37.4, 31.7, 29.0, 27.7, 24.0, 22.5, 22.0; HRFAB calcd for $C_{45}H_{52}N_4O_8$ $(M)^+$ 776.3772, found $(M+H)^+$ 777.3860. Anal. Calcd for $C_{45}H_{52}N_4O_8 \cdot H_2O$: C, 67.99; H, 6.85; N, 7.05. Found: C, 68.17; H, 6.63; N, 7.07.

Allylalanine *tert*-Butyl Ester. N^{α}-BOC-L-lysine *tert*-butyl ester was reductively aminated using known conditions[28] to afford 40% of N^{α}-BOC-N^{ϵ},N^{ϵ}-dimethyllysine *tert*-butyl ester as a clear colorless oil after chromatography: ^{1}H NMR ($CDCl_3$) δ 1.22–1.83 (m, 24 H), 2.12–2.22 (m, 8 H), 4.04–4.13 (m, 1 H), 5.08 (br d, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 155.3, 81.5, 79.4, 59.4, 53.9, 45.4, 32.6, 28.3, 28.0, 27.3, 23.0.

The above lysine derivative was oxidized using known conditions[29] to afford a nearly quantitative yield of the amine oxide monohydrate as a viscous colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30–1.93 (m, 24 H), 3.22–3.40 (m, 8 H), 4.01–4.11 (m, 1 H), 5.30 (br d, 1 H), 10.78 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 171.7, 188.0, 155.5, 81.9, 79.6, 70.2, 57.5, 57.2, 53.6, 32.3, 28.3, 28.0, 23.0, 22.4.

The amine oxide hydrate (811 mg, 2.22 mmol) was allowed to dissolve in CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 743 mg of white foam, which was allowed to dissolve in toluene (35 mL) and heated to reflux. After 5 h, TLC [silica, CH_2Cl_2–MeOH–NH_4OH (90:10:0.5)] indicated some remaining starting material (R_f ~0.2) and two new less polar materials (R_f ~0.5, 0.95, ninhydrin stain). The reaction was cooled and concentrated in vacuo affording an amber oil. The oil was flash chromatographed on 90 g of silica using ethyl acetate–hexane (10:90) and then CH_2Cl_2–MeOH–NH_4OH (95:5:0.05) to afford 122 mg (19%) of the desired allylalanine derivative followed by 228 mg (31%) of the N^{ϵ},N^{ϵ}-dimethyllysine derivative: ^{1}H NMR ($CDCl_3$) δ 1.37–2.15 (m, 22 H), 4.09–4.21 (m, 1 H), 4.91–5.08 (m, 3 H), 5.68–5.83 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 155.3, 137.3, 115.4, 81.7, 79.5, 53.5, 32.2, 29.4, 28.3, 28.0.

Compound 26. The yield of **54** was 56% as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.32–2.33 (m, 20 H), 2.69–2.79 (m, 1 H), 2.94–3.05 (m, 2 H), 3.28 (dd, 1 H), 3.81–3.98 (m, 5 H), 4.31–4.39 (m, 1 H), 4.59–4.68 (m, 1 H), 4.88–4.99 (m, 2 H), 5.60–5.75 (m, 1 H), 6.67 (br d, 1 H), 7.07–7.52 (m, 9 H), 7.82 (br d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.6, 174.2, 170.9, 170.6, 159.8, 137.3, 137.0, 129.6, 129.3, 128.5, 126.8, 120.6, 119.9, 115.3, 112.3, 81.8, 65.4, 62.1, 55.4, 54.4, 52.4, 52.2, 37.7, 31.7, 29.1, 28.0, 27.9, 24.2, 22.5; HRFAB calcd for $C_{34}H_{45}N_3O_6$ $(M)^+$ 591.3297, found $(M+H)^+$ 592.3410.

Compound 28. L-Pipecolyl-L-phenylalanyl-L-valine *tert*-butyl ester was alkylated with α-bromo-2-napthylacetophenone using general procedure C to afford 81% of compound **28** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.67 (br d, 6 H), 1.16–1.98 (m, 16 H), 2.17–2.28 (m, 1 H), 2.77–3.09 (m, 3 H), 3.28 (dd, 1 H), 4.02 (AB quart, 2 H), 4.23 (dd, 1 H), 4.59–4.68 (m, 1 H), 6.68 (br d, 1 H), 7.07–7.28 (m, 5 H), 7.51–7.62 (m, 2 H), 7.80–7.99 (m, 5 H), 8.44 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.2, 174.5, 170.9, 170.4, 137.0, 135.7, 133.4, 132.4, 129.8, 129.6, 129.2, 128.6, 128.5, 128.4, 127.7, 126.8, 126.7, 123.8, 81.7, 65.9, 62.2, 57.3, 54.7, 52.5, 37.8, 31.4, 28.7, 28.0, 27.8, 24.4, 22.7, 18.6, 17.5; HRFAB calcd for $C_{36}H_{45}N_3O_5$ $(M)^+$ 599.3348, found $(M+H)^+$ 600.3430. Anal. Calcd for $C_{36}H_{45}N_3O_5 \cdot H_2O$: C, 69.99; H, 7.67; N, 6.80. Found: C, 70.39; H, 7.27; N, 6.71.

Compound 29. Catalytic phase-transfer hydrogenolysis of CBZ-L-pipecolyl-L-phenylalanyl-L-valyl-L-phenylalanine methyl ester according to general procedure B afforded 83% of **29** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.83 (dd, 6 H), 1.14–2.11 (m, 6 H), 2.51–2.62 (m, 1 H), 2.78–2.87 (m, 1 H), 2.93–3.17 (m, 5 H), 3.67 (s, 3 H), 4.29 (dd, 1 H), 4.69–4.85 (m, 2 H), 6.83 (d, 1 H), 7.98 (d, 1 H), 7.07–7.29 (m, 10 H), 7.38 (d, 1 H); ^{13}C NMR ($CDCl_3$) 174.5, 171.8, 171.2, 170.5, 136.7, 135.9, 129.3, 129.2, 128.6, 128.5, 127.1, 126.9, 59.6, 58.5, 53.9, 53.3, 52.2, 45.4, 37.9, 37.7, 30.8, 29.6, 25.9, 23.8, 19.0, 18.0; HREI calcd for $C_{30}H_{40}N_4O_5$ $(M)^+$ 536.2989, found 536.3010.

Compound 31. Compound **29** was alkylated with α-bromo-3'-methoxyacetophenone according to general procedure C to afford 57% of **31** as a glassy colorless solid: ^{1}H NMR ($CDCl_3$) δ 2.73 (dd, 6 H), 1.24–1.79 (m, 6 H), 1.95–2.32 (m, 2 H), 2.65–2.76 (m, 1 H), 2.92–3.14 (m, 4 H), 3.22 (dd, 1 H), 3.78 (s, 3 H), 3.79–3.94 (m, 5 H), 4.15 (dd, 1 H), 4.54–4.66 (m, 1 H), 4.72–4.82 (m, 1 H), 6.40 (d, H), 6.81 (d, 1 H), 7.06–7.50 (m, 14 H), 7.91 (d, 1 H); ^{13}C NMR ($CDCl_3$) 127.1 (Q), 174.5 (Q), 171.7 (Q), 171.3 (Q), 170.4 (Q), 159.8 (Q), 137.2 (Q), 136.9 (Q), 135.8 (Q), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 126.8 (CH), 120.5 (CH), 119.9 (CH), 112.4 (CH), 65.0 (CH), 62.0 (CH_2), 58.3 (CH), 55.4 (CH_3), 54.7 (CH), 53.1 (CH), 52.2 (Q), 52.1 (CH_2), 37.7 (CH_2), 37.4 (CH_2), 30.4 (CH), 27.5 (CH_2), 23.9 (CH_2), 22.4 (CH_2), 19.9 (CH_3), 17.6 (CH_3); HRFAB calcd for $C_{39}H_{48}N_4O_7$ $(M)^+$ 684.3511, found $(M+H)^+$ 685.3658. Anal. Calcd for $C_{39}H_{48}N_4O_7 \cdot H_2O$: C, 66.65; H, 7.17; N, 7.97. Found: C, 66.96; H, 6.93; N, 7.94.

Compound 32. Compound **29** was alkylated with α-bromo-2-naphthylacetophenone according to general procedure C to afford 33% of **32** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, 6 H), 1.22–2.36 (m, 8 H), 2.72–2.83 (m, 1 H), 2.92–3.13 (m, 4 H), 3.24 (dd, 1 H), 3.64 (s, 3 H), 4.03 (AB quartet, 2 H), 4.56–4.79 (m, 2 H), 6.33 (d, 1 H), 6.80 (d, 1 H), 7.04–7.31 (m, 10 H), 7.52–7.68 (m, 2 H), 7.83–8.02 (m, 5 H), 8.46 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 197.1, 174.6, 171.5, 171.2, 170.2, 136.8, 135.7, 135.6, 132.3, 129.7, 129.5, 129.1, 128.6, 128.5, 128.4, 127.8, 127.0, 126.9, 126.8, 123.7, 65.3, 62.0, 58.2, 54.8, 53.0, 52.2, 37.6, 37.3, 30.4, 27.8, 24.0, 22.5, 18.9, 17.4; HRFAB calcd for $C_{42}H_{45}N_4O_6$ $(M)^+$ 704.3562, found $(M+H)^+$ 705.3635. Anal. Calcd for $C_{42}H_{48}N_4O_6 \cdot H_2O$: C, 69.78; H, 6.97; N, 7.75. Found: C, 69.88; H, 6.94; N, 7.55.

N^{α}-BOC-Valylacetylene 75. Unwashed sodium hydride (60% in oil, 1.56 g, 39.0 mmol) was added portionwise over 5 min to a 0 °C THF solution (200 mL) of *N*-α-BOC-valinal[19] (3.56 g, 17.7 mmol) and dimethyl diazomethylphosphonate[20] (2.79 g, 18.6 mmol) under N_2. After 15 min TLC [silica, ethyl acetate–hexane (25:75)] indicates no remaining aldehyde and one new less polar material (R_f ~0.8, UV). The reaction was quenched carefully with H_2O (150 mL) then poured onto Et_2O (150 mL). The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a pale yellow crystalline solid. This solid was flash chromatographed on 300 g of silica using ethyl acetate–hexane (5:95) as eluent to afford 2.68 g (77%) of **75** as a white crystalline solid. An analytical sample was obtained by recrystallization from hexanes: mp 59–61.5 °C (uncorrected); $[\alpha]^{20}_D$ = −57.9° (c = 1.026, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6 H), 1.43 (s, 9 H), 1.81–1.93 (m, 1 H), 2.22 (d, 1 H), 4.23–4.32 (br m, 1 H), 4.77 (br d, 1 H); ^{13}C NMR ($CDCl_3$) 154.9, 82.0, 79.8, 71.7, 48.5, 32.9, 28.3, 18.6, 17.5. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.95; H, 9.81; N, 7.06.

Compound 43. The yield of **43** was 74% as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.82 (dd, 6 H), 1.20–1.80 (m, 7 H), 2.09 (d, 1 H), 2.09–2.31 (m, 1 H), 2.65–2.76 (m, 1 H), 2.95–3.05 (m, 2 H), 2.19 (dd, 1 H), 3.76–3.92 (m, 5 H), 4.47–4.53 (m, 1 H), 4.58–4.68 (m, 1 H), 6.83 (d, 1 H), 7.07–7.28 (m, 6 H), 7.33 (t, 1 H), 7.41–7.48 (m, 2 H), 7.82 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.1, 174.3, 170.2, 159.8, 137.2, 136.9, 129.6, 129.3, 128.5, 126.8, 120.5, 120.0, 112.4, 81.3, 71.7, 65.0, 61.9, 55.4, 55.3, 52.1, 47.0, 37.4, 32.4, 27.4, 23.9, 22.4 18.7, 17.4; HREI calcd for $C_{42}H_{48}N_4O_4$ $(M)^+$ 672.3664, found 672.3710.

Compound 44. Compound **44** was obtained in 37% yield as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.83 (dd, 6 H), 1.25 (t, 3 H), 1.20–1.82 (m, 7 H), 2.20–2.34 (m, 1 H), 2.68–2.78 (m, 1 H), 2.97–3.09 (m, 2 H), 3.18 (dd, 1 H), 3.79–3.92 (m, 5 H), 4.13 (q, 2 H), 4.30–4.39 (m, 1 H), 4.58–4.68 (m, 1 H), 5.67 (d, 1 H), 6.70 (dd, 1 H), 6.82 (d, 1 H), 7.08–7.46 (m, 9 H), 7.89 (br d, 1 H); ^{13}C NMR ($CDCl_3$) δ 196.9, 174.5, 170.8, 166.1, 159.9, 146.2, 136.9, 129.6, 129.2, 128.5, 126.8, 121.7, 120.4, 119.9, 112.3, 65.0, 61.8, 60.3, 55.4, 55.2, 54.9, 52.0, 37.4, 32.0, 27.5, 23.9, 22.4, 18.7, 18.0, 14.2; HREI calcd for $C_{33}H_{43}N_3O_6$ $(M)^+$ 577.3141, found 577.3086.

Compound 72. Compound **67** was treated with HCl in ethyl acetate as in general procedure D to afford a quantitative yield of **72** as an amber oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (dd, 6 H), 2.03

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(s, 3 H), 2.05–2.20 (br m, 1 H), 3.48–3.66 (br m, 1 H), 4.55 (br d, 2 H), 5.68–6.11 (m, 2 H).

Compound 45. Compound **45** was obtained in 77% yield as an oil which crystallized slowly: ^{1}H NMR ($CDCl_3$) δ 0.72 (dd, 6 H), 1.16–1.80 (m, 5 H), 2.03 (s, 3 H), 2.19–2.32 (m, 2 H), 2.54–2.66 (m, 1 H), 2.68–2.78 (m, 1 H), 2.98–3.09 (m, 2 H), 3.22 (dd, 1 H), 3.77–3.92 (m, 5 H), 4.16–4.23 (m, 1 H), 4.42 (d, 2 H), 4.55–4.67 (m, 1 H), 5.34–5.53 (m, 2 H), 6.49 (d, 1 H), 7.06–7.48 (m, 9 H), 7.86 (br d, 1 H); ^{13}C NMR ($CDCl_3$) 197.2, 174.6, 170.9, 170.4, 137.1, 132.9, 129.7, 129.3, 128.5, 126.7, 125.3, 120.4, 119.9, 112.3, 64.9, 64.3, 61.8, 55.5, 55.4, 54.8, 52.0, 37.4, 32.1, 27.4, 23.9, 22.4, 20.9, 18.6, 18.1; HREI calcd for $C_{33}H_{43}N_3O_6$ $(M)^+$ 577.3141, found 577.3134.

Compound 46. Compound **46** was obtained in 57% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 6 H), 1.17–1.83 (m, 7 H), 2.01 (s, 3 H), 2.23–2.38 (m, 1 H), 2.72–2.84 (m, 1 H), 2.99–3.12 (m, 2 H), 3.21 (dd, 1 H), 4.01 (AB quart, 2 H), 4.12–4.22 (m, 1 H), 4.38–4.41 (m, 2 H), 4.54–4.64 (m, 1 H), 5.31–5.50 (m, 2 H), 6.42 (d, 1 H), 7.17–7.26 (m, 5 H), 7.51–7.64 (m, 2 H), 7.85–7.99 (m, 5 H), 8.41 (s, 1 H); ^{13}C NMR ($CDCl_3$) 197.2, 174.7, 170.9, 170.4, 137.1, 135.7, 132.8, 132.4, 129.6, 129.3, 128.7, 128.6, 128.5, 127.8, 127.0, 126.7, 125.2, 123.6, 65.2, 64.3, 61.8, 55.4, 54.9, 52.2, 37.4, 32.1, 27.7, 24.0, 22.5, 20.9, 18.5; 18.0; HREI calcd for $C_{36}H_{43}N_3O_5$ $(M)^+$ 597.3192, found 597.3184.

Hydrozirconation of Terminal Acetylenes Using the Lipshutz Method. A flame-dried 125-mL flask with stir bar, cooled under nitrogen, was charged with Cp_2ZrCl_2 (1.48 g, 5.06 mmol, 2.5 equiv) followed by CH_2Cl_2 (50 mL). To this solution was added, dropwise over approximately 5 min, 5.10 mL of a 1.0 M solution of $LiEt_3BH$ in THF ("Super-Hydride", Aldrich). The insoluble mixture (white precipitate) was allowed to stir shielded from light for 1 h at ambient temperature. After this time, **75** (400 mg, 2.03 mmol) was added in one portion. This mixture was stirred for 1.5 h (pale yellow color observed). The reaction was quenched by the addition of iodine (1.03 g, 8.12 mmol, 4 equiv) in one portion (deep iodine color observed). This mixture was stirred for 1 h. The reaction was poured into ~75 mL of saturated aqueous $NaHCO_3$, the layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a yellow oily solid (824 mg). The crude product **78** was purified by flash chromatography on 85 g of silica eluted with ethyl acetate–hexane (5:95). The yield of colorless crystalline **78** was 335 mg (51%; mp 89–90 °C); $[\alpha]^{21}_D$ = −54.7° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (d, 6 H), 1.41 (s, 9 H), 1.73 (m, 1 H), 3.94 (broad s, 1 H), 4.64 (broad d, 1 H), 6.20 (d, 1 H), 6.39 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.3 (C=O), 145.1 (CH), 79.6 (Q), 77.3 (CH), 60.3 (CH), 32.1 (CH), 28.4 (CH_3), 18.7 (CH_3), 18.2 (CH_3); HREI calcd for $C_{11}H_{20}INO_2$ $(M)^+$ 325.0533, found $(M)^+$ 325.0542.

Nickel-Catalyzed Conjugate Addition of Alkenyl Zirconium Species to α,β-Unsaturated Ketones Using the Schwartz Method. A flame-dried 50-mL flask with stir bar, cooled under nitrogen, was charged with Cp_2ZrCl_2 (1.87 g, 6.40 mmol, 2.5 equiv) followed by (10 mL) THF. To this solution was added, dropwise over approximately five min, 6.40 mL of a 1.0 M solution of $LiEt_3BH$ in THF. The colorless solution (slightly turbid) was allowed to stir shielded from light for 1 h at ambient temperature. After this time, **75** (500 mg, 2.53 mmol) was added in one portion. This mixture was stirred for 20 min (became a clear yellow solution) after which time 5,6-dihydro-2*H*-pyran-2-one was added (437 mL, 5.07 mmol, 2 equiv) dropwise. The resulting solution was stirred for 10 min.

In a second 125-mL flask (flame-dried), $Ni(AcAc)_2$ (82 mg, 0.319 mmol, 12.5%) was dissolved in THF (5 mL), cooled to 0 °C, and exposed to DIBAH (320 μL of 1.0 M heptane solution). To this solution was added (via cannula) the freshly prepared vinyl zirconium reagent, and the resulting mixture was stirred at 0 °C for 3 h. After this time, a second portion of "activated" $Ni(AcAc)_2$ (82 mg, 0.319 mmol, 12.5% with 320 mL of a 1.0 M solution of DIBAH in heptane at 0 °C) was added via cannula, and the mixture was stirred for an additional 3 h at 0 °C.

The reaction was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous $MgSO_4$. Concentration in vacuo afforded a cloudy yellow oil (1.24 g). The crude product was purified by flash chromatography over 250 g of silica eluted with CH_2Cl_2–MeOH (99:1) and then CH_2Cl_2–MeOH (98:2), affording 404 mg (54% yield) of **81**: ^{1}H NMR ($CHCl_3$) δ 0.85 (d, 6 H), 1.41 (s, 9 H), 1.68 (m, 2 H), 1.84 (m, 2 H), 2.53 (m, 1 H), 2.67 (m, 1 H), 3.88 (broad s, 1 H), 4.55 (broad d, 1 H), 5.36 (dd, 1 H), 5.50 (dd, 1 H); ^{13}C NMR ($CHCl_3$) δ 171.4 (C=O), 170.5 (C=O), 155.6 (C=O), 132.4 (broad CH), 130.0 (broad CH), 79.3 (broad Q), 68.1 (broad CH_2O), 57.4 (broad CH), 35.9 (CH_2), 34.0 (CH), 32.4 (CH), 28.9 (CH_2), 28.4 (CH_3), 18.7 (CH_3), 18.2 (CH_3); HREI calcd for $C_{16}H_{27}NO_4$ $(M)^+$ 297.1933, found $(M)^+$ 297.1940.

Compounds 79 and 80 were prepared using the same procedure as for compound **81**. The yield of **79** was 38%: ^{1}H NMR ($CDCl_3$) δ 0.82 (dd, 6 H), 0.95 (d, 3 H), 1.36 (s, 9 H), 1.56 (m, 1 H), 2.05 (s, 3 H), 2.35 (m, 2 H), 2.66 (m, 1 H), 3.83 (broad d, 1 H), 4.46 (broad d, 1 H), 5.24 (dd, 1 H), 5.41 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 207.9 (C=O), 155.4 (C=O), 135.6 (broad CH), 128.0 (broad CH), 79.0 (Q), 57.4 (broad CH), 50.7 (broad CH_2), 32.5 (broad CH), 30.6 (broad CH_3), 28.4 (CH_3), 20.3 (CH_3), 18.6 (CH_3), 18.2 (CH_3); HREI calcd for $C_{16}H_{29}NO_3$ $(M)^+$ 283.2140, found (M + H) 284.2241.

The yield of **80** was 51%: ^{1}H NMR ($CDCl_3$) δ 0.83 (dd, 6 H), 1.39 (s, 9 H), 1.70 (m, 1 H), 1.99 (m, 2 H), 2.14 (m, 2 H), 2.30 (m, 2 H), 2.83 (m, 1 H), 3.88 (broad d, 1 H), 4.52 (broad d, 1 H), 5.35 (dd, 1 H), 5.58 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.7 (C=O), 155.5 (C=O), 133.2 (CH), 129.1 (broad CH), 79.2 (Q), 57.3 (CH), 44.7, 39.4, 38.0, 32.5, 29.8, 28.4 (CH_3), 18.7 (CH_3), 18.2 (CH_3); HREI calcd for $C_{16}H_{27}NO_3$ $(M)^+$ 281.1984, found $(M)^+$ 281.1982.

The yield of **11** was 25%: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.52–1.77 (m, 5 H), 1.93 (m, 1 H), 2.10 (m, 1 H), 2.85 (dd, 1 H), 2.99 (m, 2 H), 3.15 (dd, 1 H), 3.59 (dd, 2 H), 3.84 (s, 3 H), 4.75 (m, 1 H), 6.81–7.71 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 193.5 (C=O), 171.5 (Q), 168.1 (Q), 157.3 (Q), 134.7 (Q), 134.1 (Q), 127.0 (CH), 126.3 (CH), 125.7 (CH), 124.0 (CH), 118.0 (CH), 117.3 (CH), 109.7 (CH), 79.4 (Q), 64.1 (CH), 59.7 (CH_2), 52.9 (OCH_3), 50.7 (CH), 50.2 (CH_2), 35.2 (CH_2), 27.0 (CH_2), 25.4 (CH_3), 21.9 (CH_2), 20.5 (CH_2); HREI calcd for $C_{28}H_{36}N_2O_5$ $(M)^+$ 480.2615, found $(M)^+$ 480.2612.

The yield of **13** was 68%: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9 H), 1.36–1.78 (m, 17 H), 1.96 (m, 1 H), 2.16 (m, 1 H), 3.02 (m, 2 H), 3.74 (d, 1 H), 3.79 (s, 3 H), 4.20 (m, 1 H), 4.38 (m, 1 H), 7.02 (dd, 1 H), 7.19 (broad d, 1 H), 7.28 (dd, 1 H), 7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.1 (C=O), 174.2 (Q), 171.8 (Q), 159.7 (Q), 137.6 (Q), 129.4 (CH), 120.4 (CH), 119.6 (CH), 112.1 (CH), 81.2 (Q), 67.1, 62.5, 53.1, 50.1, 39.2, 34.4, 33.4, 32.2, 30.5, 27.8 (CH_3), 26.4, 26.2, 26.1, 24.8, 23.3; HREI calcd for $C_{28}H_{42}N_2O_5$ $(M)^+$ 486.3083, found $(M)^+$ 486.3084.

The yield of **15** was 76%: ^{1}H NMR δ 1.25 (s, 9 H), 1.34–1.70 (m, 5 H), 1.85 (m, 1 H), 2.18 (m, 1 H), 2.98 (m, 3 H), 3.13 (dd, 1 H), 3.72 (d, 1 H), 3.80 (s, 3 H), 4.09 (d, 1 H), 4.63 (m, 1 H), 6.88–7.47 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 1.96.8 (C=O), 173.9 (Q), 170.4 (Q), 159.7 (Q), 137.6 (Q), 136.8 (Q), 129.5 (CH), 128.3 (CH), 125.6 (CH), 122.4 (CH), 120.5 (CH), 119.7 (CH), 112.1 (CH), 81.8 (Q), 66.6 (CH), 62.3 (CH_2), 55.4 (OCH_3), 52.7 (CH_2), 52.6 (CH), 32.3 (CH_2), 29.8 (CH_2), 27.8 (CH_3), 24.7 (CH_2), 23.1 (CH_2); HREI calcd for $C_{26}H_{34}N_2O_5S$ $(M)^+$ 486.2179, found $(M)^+$ 486.2196.

The yield of **16** was 82%: ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.47–1.73 (m, 5 H), 1.89 (m, 1 H), 2.19 (m, 1 H), 2.99 (m, 2 H), 3.26 (m, 2 H), 3.72 (d, 1 H), 3.80 (s, 3 H), 4.08 (d, 1 H), 4.64 (m, 1 H), 6.84 (m, 2 H), 7.06 (m, 2 H), 7.29 (dd, 1 H), 7.42 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.7 (C=O), 174.0 (Q), 169.8 (Q), 159.7 (Q), 138.3 (Q), 137.6 (Q), 129.5 (CH), 126.7 (CH), 126.5 (CH), 124.4 (CH), 120.5 (CH), 119.6 (CH), 112.1 (CH), 82.1 (Q), 66.7 (CH), 62.3 (CH_2), 55.4 (OCH_3), 53.2 (CH_2), 52.7 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 27.8 (CH_3), 24.7 (CH_2), 23.1 (CH_2); HREI calcd for $C_{26}H_{34}N_2O_5S$ $(M)^+$ 486.2179, found $(M)^+$ 486.2193.

The yield of **18** was 86%: ^{1}H NMR ($CDCl_3$) δ 0.88 (dd, 6 H), 1.26 (s, 9 H), 1.39–1.79 (m, 4 H), 1.95–2.29 (m, 4 H), 3.07 (m, 2 H), 3.77 (d, 1 H), 3.81 (s, 3 H), 4.17 (d, 1 H), 4.28 (dd, 1 H), 7.03 (dd, 1 H), 7.29 (m, 2 H), 7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.5 (C=O), 174.3 (Q), 170.6 (Q), 159.7 (Q), 137.6 (Q), 129.4 (CH), 120.4 (CH), 119.6 (CH), 112.0 (CH), 81.4 (Q), 67.0, 62.4, 57.2, 55.4 (OCH_3), 53.0, 30.5 (broad), 27.8, 24.8, 23.2, 19.2 (CH_3), 17.6 (CH_3); HREI calcd for $C_{24}H_{36}N_2O_5$ $(M)^+$ 432.2615, found $(M)^+$ 432.2651.

The yield of **19** was 53%: ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 6 H), 1.25 (s, 9 H), 1.30–1.90 (m, 8 H), 2.01 (m, 1 H), 2.20 (m, 1 H), 3.05 (m, 2 H), 3.76 (d, 1 H), 3.81 (s, 3 H), 4.18 (d, 1 H), 4.31 (dd, 1 H), 7.05 (m, 1 H), 7.30 (m, 2 H), 7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.5 (C=O), 174.4 (Q), 170.6 (Q), 159.7 (Q), 137.6 (Q), 129.4 (CH), 120.4 (CH), 119.6 (CH), 112.0 (CH), 81.4 (Q), 67.0, 62.4, 56.6, 55.4 (OCH_3), 53.0, 37.2, 30.5, 27.8 (CH_3), 25.1, 24.8, 23.2, 15.7, 11.7; HREI calcd for $C_{35}H_{38}N_2O_5$ $(M)^+$ 446.2771, found $(M)^+$ 446.2762.

The yield of **24** was 50%: ^{1}H NMR ($CDCl_3$) δ 1.08–1.32 (m, 2 H), 1.41–1.74 (m, 13 H), 2.27 (m, 4 H), 2.60 (m, 1 H), 2.74 (m, 1 H), 2.98 (m, 2 H), 3.26 (dd, 1 H), 3.88 (m, 5 H), 4.37 (m, 1 H), 4.67 (m, 1 H), 6.62 (broad d, 1 H), 7.08–7.51 (m, 9 H), 7.28 (broad d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.6 (C=O), 174.3 (Q), 171.8 (Q), 170.8 (Q), 160.0 (Q), 137.6 (Q), 137.2 (Q), 129.7 (CH), 129.4 (CH), 128.7 (CH), 126.9 (CH), 120.8 (CH), 120.0 (CH), 112.6 (CH), 81.7 (Q), 65.6 (CH), 62.2 (CH_2), 55.6 (OCH_3), 54.5 (CH), 52.4 (CH_2), 50.9 (CH), 40.3 (CH_2), 37.8 (CH_2), 34.3 (CH), 33.4 (CH_2), 32.9 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 24.3 (CH_2), 22.7 (CH_2); HREI calcd for $C_{37}H_{51}N_3O_6$ $(M)^+$ 633.3765, found $(M)^+$ 633.3836.

The yield of **27** was 72%: ^{1}H NMR ($CDCl_3$) δ 1.06 (m, 2 H), 1.28 (s, 9 H), 1.37–1.80 (m, 13 H), 2.28 (m, 4 H), 2.60 (m, 1 H), 2.82 (broad d, 1 H), 3.03 (m, 2 H), 3.30 (dd, 1 H), 4.07 (m, 2 H), 4.38 (m, 1 H), 4.71 (m, 1 H), 6.69 (broad d, 1 H), 7.19 (m, 5 H), 7.58 (m, 2 H), 7.87 (m, 3 H), 7.98 (m, 2 H), 8.48 (broad s, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.5 (C=O), 174.2 (Q), 171.6 (Q), 170.6 (Q), 137.0 (Q), 135.7 (Q), 133.4 (Q), 132.4 (Q), 129.8 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 127.7 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 123.7 (CH), 81.4 (Q), 65.7 (CH), 62.0 (CH_2), 54.3 (CH), 52.4 (CH_2), 50.7 (CH), 40.1 (CH_2), 37.7 (CH_2), 34.0 (CH), 33.1 (CH_2), 32.7 (CH_2), 28.2 (CH_2), 27.8 (CH_3), 26.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.2 (CH_2), 22.6 (CH_2); HRFAB calcd for $C_{40}H_{51}N_3O_5$ $(M)^+$ 653.3816, found $(M + H)^+$ 654.3921.

The yield of **49** was 29%: ^{1}H NMR ($CDCl_3$) δ 0.69 (m, 6 H), 0.92 (m, 6 H), 1.27–1.77 (m, 4 H), 2.06 (d, 3 H), 2.20–2.76 (m, 5 H), 3.01 (m, 2 H), 3.21 (dd, 1 H), 3.83 (m, 5 H), 4.09 (m, 1 H), 4.59 (m, 1 H), 5.11 (dd, 1 H), 5.27 (m, 1 H), 6.40 (broad d, 1 H), 7.07–7.48 (m, 9 H), 7.86 (broad d, 1 H); ^{13}C NMR ($CDCl_3$) δ 196.8 (C=O), 174.3 (Q), 170.2 (Q), 170.1 (Q), 159.8 (Q), 137.1, 136.2, 129.7, 129.3, 128.5, 126.9, 126.7, 120.4, 119.9, 112.3, 64.9, 61.9, 56.0, 55.4 (OCH_3), 54.7, 52.0, 50.5, 37.4, 32.3, 32.2, 27.4, 23.9, 22.4, 20.1, 18.4 (CH_3), 18.2 (CH_3); HREI calcd for $C_{35}H_{47}N_3O_5$ $(M)^+$ 589.3504, found $(M)^+$ 589.3472.

The yield of **50** was 50%: ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 6 H), 1.21–2.33 (m, 13 H), 2.68 (m, 2 H), 3.01 (m, 2 H), 3.21 (dd, 1 H), 3.85 (m, 5 H), 4.16 (m, 2 H), 4.62 (m, 1 H), 5.18 (m, 1 H), 5.37 (m, 1 H), 6.54 (broad d, 1 H), 7.04–7.47 (m, 9 H), 7.82 (broad d, 1 H); ^{13}C NMR ($CDCl_3$) δ 218.7 (C=O), 196.9 (C=O), 174.2 (Q), 170.3 (Q), 167.7 (Q), 159.8 (Q), 137.1 (Q), 133.6 (CH), 129.7 (CH), 129.3 (CH), 128.5 (CH), 128.2 (CH), 126.7 (CH), 120.4 (CH), 119.8 (CH), 112.4 (CH), 68.1 (CH_2), 64.8 (CH), 61.8 (CH_2), 55.8 (CH), 55.4 (OCH_3), 54.6 (CH), 52.0 (CH_2), 38.7 (CH), 37.5 (CH_2), 32.2 (CH), 27.3 (CH_2), 27.2 (CH_2), 23.9 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 18.5 (CH_3), 18.2 (CH_3); HREI calcd for $C_{35}H_{45}N_3O_5$ $(M)^+$ 587.3348, found $(M)^+$ 587.3399.

The yield of **51** was 16%: ^{1}H NMR ($CDCl_3$) δ 0.69 (m, 6 H), 1.21–2.40 (m, 13 H), 2.66–3.09 (m, 4 H), 3.17 (m, 1 H), 3.63–4.22 (m, 7 H), 4.59 (m, 1 H), 5.07 (m, 1 H), 5.28 (m, 1 H), 6.69 (broad d, 1 H), 7.05–7.88 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 170.3, 167.7, 159.7, 137.4, 129.6, 129.3, 129.1, 128.5, 128.4, 126.9, 120.5, 119.7, 112.3, 66.5, 62.9, 56.3, 55.4 (OCH_3), 52.1, 40.1, 37.7, 37.4, 36.3, 32.2, 29.0, 24.8, 22.1, 18.7 (CH_3), 18.3 (CH_3); HREI calcd for $C_{35}H_{46}N_3O_6$ $(M)^+$ 603.3297, found $(M)^+$ 603.3339.

The yield of **54** was 46%: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H), 1.39–1.80 (m, 6 H), 2.33 (m, 1 H), 2.77 (m, 1 H), 3.02 (m, 2 H), 3.29 (dd, 1 H), 3.89 (m, 5 H), 4.38 (m, 1 H), 4.62 (m, 1 H), 5.96 (d, 1 H), 6.26 (dd, 1 H), 6.47 (broad d, 1 H), 7.10–7.52 (m, 9 H), 7.87 (broad d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.2 (C=O), 174.1 (Q), 170.1 (Q), 159.9 (Q), 146.2 (CH), 137.1 (Q), 136.8 (Q), 129.7 (CH), 129.3 (CH), 128.6 (CH), 126.9 (CH), 120.4 (CH), 119.9 (CH), 112.4 (CH), 77.2 (CH), 64.9 (CH), 61.8 (CH_2), 55.5 (OCH_3), 54.5 (CH), 52.1 (CH_2), 48.9 (CH), 37.8 (CH_2), 27.1 (CH_2), 22.4 (CH_2), 19.7 (CH_3); HREI calcd for $C_{28}H_{34}IN_3O$ $(M)^+$ 603.1593, found $(M)^+$ 603.1557.

Compound 22. Compound **22** was obtained in 68% yield as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.80 (dd, 6 H), 1.20–1.86 (m, 18 H), 2.14–2.27 (m, 1 H), 2.68–2.78 (m, 1 H), 2.92–3.03 (m, 2 H), 3.26 (dd, 1 H), 3.78–3.95 (m, 5 H), 4.29–4.39 (m, 1 H), 4.60–4.70 (m, 1 H), 6.63 (d, 1 H), 7.07–7.49 (m, 9 H), 7.77 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.3, 174.3, 171.6, 170.6, 159.8, 137.3, 137.0, 129.6, 129.2, 128.5, 126.7, 120.6, 119.9, 112.3, 81.6, 65.4, 62.0, 55.4, 54.3, 52.3, 51.2, 41.6, 37.6, 28.0, 27.9, 24.7, 24.1, 22.7, 22.5, 22.0; HRFAB calcd for $C_{34}H_{47}N_3O_6$ $(M)^+$ 593.3453, found (M + H) 594.3566.

Compound 47. Compound **66** was saponified with LiOH in THF–H_2O to afford the acid which was coupled with (*S*)-(−)-methylbenzylamine according to general procedure A to give the methylbenzylamide in 90% yield as a white solid: ^{1}H NMR (CDO_3) δ 0.84 (d, 6 H), 1.38 (s, 9 H), 1.43 (d, 3 H), 1.67–1.80 (m, 1 H), 3.92–4.01 (m, 1 H), 4.97–4.16 (m, 2 H), 5.88 (d, 1 H), 6.59 (dd, 1 H), 7.15–7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$ + MeOH-d_4) 164.8, 155.7, 143.2, 142.6, 128.5, 127.2, 126.2, 124.4, 79.6, 57.2, 48.7, 32.3, 28.3, 21.6, 18.8, 18.1.

Compound **47** was obtained from the above amide in 28% yield as a glossy solid: ^{1}H NMR ($CDCl_3$) δ 0.72 (dd, 6 H), 1.17–2.40 (m, 10 H), 2.72–2.82 (m, 1 H), 2.93–3.13 (m, 3 H), 3.12 (dd, 1 H), 4.04 (AB quartet, 2 H), 4.27–4.41 (m, 1 H), 4.57–4.67 (m, 1 H), 5.09–5.22 (m, 1 H), 5.43 (d, 1 H), 5.74 (d, 1 H), 6.44 (d, 1 H), 6.65 (dd, 1 H), 7.08–7.39 (m, 10 H), 7.52–7.67 (m, 2 H), 7.82–8.06 (m, 5 H), 8.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) 197.2, 174.6, 170.7, 164.2, 143.1, 142.3, 137.2, 135.9, 133.3, 132.6, 129.6, 129.4, 128.6, 127.8, 127.4, 127.0, 126.7, 126.3, 123.8, 123.6, 67.1, 64.9, 61.8, 55.1, 55.0, 52.0, 48.8, 37.3, 31.9, 27.2, 23.9, 21.5, 14.7, 17.9; HREI calcd for $C_{42}H_{48}N_4O_4$ $(M)^+$ 672.3664, found 672.3710.

Compound 48. Compound **48** was obtained in 22% yield as a glossy solid: ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, 6 H), 1.18–1.61 (m, 8 H), 1.67–1.79 (m, 1 H), 2.20–2.36 (m, 2 H), 2.66–2.76 (m, 1 H), 2.96–3.08 (m, 2 H), 3.24 (dd, 1 H), 3.78–3.91 (m, 5 H), 4.31–4.39 (m, 1 H), 4.57–4.66 (m, 1 H), 5.10–5.20 (m, 1 H), 5.48 (d, 1 H), 5.39 (d, 1 H), 6.50 (d, 1 H), 6.67 (dd, 1 H), 6.98–7.47 (m, 14 H), 7.98 (d, 1 H); ^{13}C NMR ($CDCl_3$) 196.9, 174.5, 170.6, 164.1, 159.9, 143.0, 142.3, 137.1, 129.7, 129.4, 128.7, 128.6, 127.4, 126.7, 126.3, 123.9, 120.4, 120.0, 112.3, 64.6, 61.8, 55.4, 55.2, 54.9, 51.9, 48.8, 37.3, 32.0, 26.9, 23.7, 22.3, 21.5, 18.8, 18.0; HREI calcd for $C_{39}H_{48}N_4O_5$ $(M)^+$ 652.3583, found 652.3621.

Compound 53. Neat trifluoroacetic anhydride (117 mg, 0.559 mmol) was added dropwise to a 0 °C CH_2Cl_2 (3 mL) solution of **67** (120 mg, 0.523 mmol) and triethylamine (57.7 mg, 0.570 mmol) under N_2. After 1.5 h, TLC [ethyl acetate–hexane (25:75)] indicated no remaining **67** and one new less polar material (R_f ~0.6, UV, $KMnO_4$ stain). The reaction was washed with 0.1 N HCl and aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo afforded 154 mg (90%) of the trifluoroacetate as a light amber oil: ^{1}H NMR ($CDCl_3$) δ 2.88 (dd, 6 H), 1.42 (s, 9 H), 1.67–1.84 (m, 1 H), 4.02 (br s, 1 H), 4.55 (br d, 1 H), 4.79 (d, 2 H), 5.63–5.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.4, 137.4, 122.1, 116.7, 79.5, 67.8, 56.8, 32.2, 28.3, 18.7, 18.0.

Chain extension via the N-terminus afforded **53** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.72 (dd, 6 H), 1.23–1.79 (m, 7 H), 2.18–2.32 (m, 1 H), 2.65–2.76 (m, 1 H), 2.99–3.09 (m, 2 H), 3.22 (dd, 1 H), 3.77–3.92 (m, 5 H), 4.16–4.27 (m, 1 H), 4.54–4.63 (m, 1 H), 4.68 (d, 2 H), 5.38 (dt, 1 H), 5.63 (dd, 1 H), 6.46 (d, 1 H), 7.09–7.48 (m, 9 H), 7.88 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 196.9, 174.4, 170.6, 159.9, 137.0, 136.1, 129.7, 129.3, 128.6, 126.8, 122.5, 120.4, 119.9, 112.4, 67.6, 64.8, 61.8, 55.4, 55.3, 54.9, 52.1, 37.3, 32.0, 27.2, 23.8, 22.4, 18.6, 18.0; HREI calcd for $C_{33}H_{40}F_3N_3O_6$ $(M)^+$ 631.2859, found 631.2889.

Compound 52. Compound **67** was treated with benzoyl chloride in analogous fashion to the trifluoroacetate above, which was further elaborated by the standard sequence to afford **52** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 0.74 (dd, 6 H), 1.17–1.82 (m, 7 H), 2.21–2.33 (m, 1 H), 2.66–2.77 (m, 1 H), 2.98–3.09 (m, 2 H), 3.23 (dd, 1 H), 3.76–3.94 (m, 5 H), 4.20–4.30 (m, 1 H), 4.57–4.72 (m, 3 H), 4.46–4.66 (m, 2 H), 6.47 (d, 1 H), 7.09–7.49 (m, 10 H), 7.86 (d, 1 H), 7.99–8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.9, 174.3, 170.4, 166.2, 159.8, 137.1, 133.0, 132.9, 129.6, 129.5, 129.3, 128.5, 128.3, 126.7, 125.2, 119.9, 112.3, 64.9, 64.8, 61.8, 55.5, 55.4, 54.9, 52.0, 37.4, 32.1, 27.3, 23.9, 22.4, 18.6, 18.1; HREI calcd for $C_{35}H_{45}N_3O_6$ $(M)^+$ 639.3297, found 639.3312.

Compound 55. Unwashed sodium hydride (60% in oil, 10 mg, 0.250 mmol) was added to a 0 °C THF (2 mL) solution of

67 (115 mg, 0.500 mmol) under N_2. After 15 min, allyl bromide (60 mg, 0.500 mmol) was added neat and the reaction was allowed to stir overnight. TLC [ethyl acetate–hexane (25:75)] indicated no remaining 67 and one new less polar material (R_f ~0.6, UV, $KMnO_4$ stain). The reaction was poured onto Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with Et_2O (2 × 5 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to an amber oil. The oil was flash chromatographed on 40 g of silica using ethyl acetate–hexane (10:90) as eluent to afford 50 mg (37%) of the allyl ether as a clear, colorless oil: ^1H NMR ($CDCl_3$) δ 0.88 (dd, 6 H), 1.43 (s, 9 H), 1.57–1.83 (m, 1 H), 3.93–3.99 (m, 5 H), 4.52 (br d, 1 H), 5.13–5.30 (m, 2 H), 5.54–5.73 (m, 2 H), 5.82–5.98 (m, 1 H); ^{13}C NMR ($CDCl_3$) 155.5, 134.7, 132.2, 127.4, 117.0, 79.2, 70.9, 70.1, 56.9, 32.4, 28.4, 18.7, 18.1.

Chain extension via the N-terminus afforded **55** as a glassy solid: ^1H NMR ($CDCl_3$) δ 0.72 (d, 6 H), 1.14–1.83 (m, 7 H), 2.15–2.38 (m, 1 H), 2.66–2.83 (m, 1 H), 2.96–3.09 (m, 2 H), 3.12 (dd, 1 H), 3.73–3.99 (m, 9 H), 4.13–4.24 (m, 1 H), 4.54–4.66 (m, 1 H), 5.12–5.29 (m, 2 H), 5.42–5.49 (m, 2 H), 5.78–5.96 (m, 1 H), 6.46 (d, 1 H), 7.09–7.49 (m, 9 H), 7.86 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 196.9, 174.3, 170.3, 159.9, 137.1, 134.7, 131.0, 129.6, 129.3, 128.5, 127.9, 126.7, 120.4, 120.0, 116.9, 112.3, 70.9, 70.0, 65.0, 61.7, 55.7, 55.4, 54.8, 52.1, 37.4, 32.2, 27.5, 23.9, 22.4, 18.6, 18.1; HREI calcd for $C_{34}H_{45}N_3O_5$ $(M)^+$ 575.3348, found 575.3341.

Compound 56. A solution of benzylmagnesium chloride (1.0 M in Et_2O, 15.0 mL, 15.0 mmol) was added dropwise over ~5 min to a 0 °C THF (15 mL) solution of 64 (1.30 g, 5.00 mmol) under N_2. After 1 h, TLC [ethyl acetate–hexane (25:75)] indicated no remaining 64 and one new less polar material (R_f ~0.65, UV, $KMnO_4$ stain). The reaction was quenched with dropwise addition of 1 N HCl (20 mL) and poured onto Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an oil. The oil was flash chromatographed on 75 g of silica using ethyl acetate–hexane (10:90) as eluent affording 1.01 g (69%) of the benzyl ketone as an off-white crystalline solid: ^1H NMR ($CDCl_3$) δ 0.76, 0.97 (2 d, 6 H), 1.42 (s, 9 H), 2.13–2.28 (m, 1 H), 3.79 (AB quart, 2 H), 4.38 (dd, 1 H), 5.11 (d, 1 H), 7.15–7.36 (m, 5 H).

Chain extension via the N-terminus afforded compound **56** as a glassy solid: ^1H NMR ($CDCl_3$) δ 0.59, 0.79 (2 d, 6 H), 1.20–1.78 (m, 6 H), 2.02–2.8 (m, 2 H), 2.69–2.81 (m, 2 H), 2.93–3.04 (m, 2 H), 3.22 (dd, 1 H), 3.63 (AB quart, 2 H), 3.77–3.98 (m, 5 H), 4.52 (dd, 1 H), 4.57–4.68 (m, 1 H), 6.86 (d, 1 H), 7.04–7.47 (m, 14 H), 7.87 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 205.7 (Q), 197.1 (Q), 174.4 (Q), 171.4 (Q), 159.8 (Q), 136.9 (Q), 133.2 (Q), 129.5 (CH), 129.2 (CH), 128.5 (CH), 127.0 (CH), 126.8 (CH), 120.5 (CH), 120.0 (CH), 112.2 (CH), 65.3 (CH), 62.3 (CH), 60.4 (CH_2), 55.4 (CH_3), 54.8 (CH), 5.23 (CH_2), 47.3 (CH_2), 47.3 (CH_3), 37.6 (CH_2), 37.6 (CH_2), 29.8 (CH), 27.9 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 19.7 (CH_3), 16.8 (CH_3); HREI calcd for $C_{36}H_{43}N_3O_5$ $(M)^+$ 597.3192, found 597.3147.

The yield of **33** was 85%: ^1H NMR (DMSO) δ 0.78 (dd, 6 H), 1.10–1.69 (m, 9 H), 1.90 (m, 1 H), 2.13 (m, 1 H), 2.69 (m, 2 H), 2.96 (m, 3 H), 3.57 (s, 3 H), 4.21 (dd, 1 H), 4.48 (m, 1 H), 4.70 (m, 1 H), 7.03 (broad d, 1 H), 7.13 (m, 2 H), 7.25 (m, 8 H), 7.42–7.59 (m, 3 H), 7.78 (m, 4 H), 7.88 (broad d, 1 H), 8.06 (m, 2 H), 8.49 (broad d, 1 H); ^{13}C NMR (DMSO) δ 172.4, 171.8, 170.9, 139.0, 137.8, 137.1, 134.5, 129.1, 129.0, 128.3, 127.9, 127.0, 126.6, 126.5, 126.2, 65.8, 62.0, 57.1, 53.5, 53.2, 51.7, 37.6, 36.5, 31.1, 29.0, 28.7, 27.6, 22.1, 19.0, 17.8; high-resolution mass spectrum, *m/e* 730.3729 (P^+, $C_{44}H_{50}N_4O_6$); HRFAB calcd for $C_{44}H_{50}N_4O_6$ $(M)^+$ 730.3718, found $(M + H)^+$ 731.3811.

The yield of **34** was 45%: ^1H NMR ($CDCl_3$) δ 0.75 (dd, 6 H), 0.88 (m, 1 H), 1.30 (m, 1 H), 1.37 (s, 9 H), 1.38–1.78 (m, 4 H), 2.02 (m, 1 H), 2.27 (m, 2 H), 2.72 (m, 1 H), 3.01 (m, 3 H), 3.22 (dd, 1 H), 3.84 (m, 8 H), 4.18 (dd, 1 H), 4.64 (m, 2 H), 6.49 (broad d, 1 H), 6.88 (broad d, 1 H), 7.08–7.50 (m, 14 H), 7.88 (broad d, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.1 (C=O), 174.5, 171.2, 170.2, 170.1, 159.8, 137.3, 136.9, 136.1, 129.6, 129.4, 129.2, 128.6, 128.4, 126.9, 126.8, 120.6, 119.9, 112.4, 82.2 (Q), 65.1, 62.0, 58.3, 55.4, 54.7, 53.6, 52.1, 38.0, 37.4, 30.6, 27.9 (CH_3), 27.6, 24.0, 22.5, 19.1 (CH_3), 17.6 (CH_3); HRFAB calcd for $C_{42}H_{54}N_4O_7$ $(M)^+$ 726.3979, found $(M)^+$ 726.3927.

The yield of **35** was 53%: ^1H NMR ($CDCl_3$) δ 0.68 (dd, 6 H), 0.87 (m, 1 H), 1.24–1.58 (m, 13 H), 1.75 (m, 1 H), 1.94 (m, 1 H), 2.27 (m, 1 H), 2.80 (m, 1 H), 3.00 (m, 4 H), 3.22 (dd, 1 H), 3.99 (m, 2 H), 4.16 (dd, 1 H), 4.65 (m, 2 H), 6.41 (broad d, 1 H), 6.90 (broad d, 1 H), 7.08–7.28 (m, 10 H), 7.58 (m, 2 H), 7.92 (m, 5 H), 8.45 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.3 (C=O), 174.5, 171.2, 170.2, 170.1, 136.9, 136.1, 135.7, 133.3, 132.4, 129.8, 129.6, 129.4, 129.2, 128.6, 128.5, 128.45, 128.4, 127.8, 126.9, 126.8, 123.8, 82.2 (Q), 65.5, 62.0, 58.3, 54.7, 53.6, 52.3, 38.0, 37.5, 30.7, 28.1, 27.9 (CH_3), 24.1, 22.6, 19.0 (CH_3), 17.7 (CH_3); HRFAB calcd for $C_{45}H_{54}N_4O_6$ $(M)^+$ 746.4030, found $(M + H)^+$ 747.4098.

The yield of **36** was 43%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.61 (dd, 6 H), 0.92 (m, 2 H), 1.26–1.87 (m, 11 H), 2.64 (m, 1 H), 2.71–3.16 (m, 5 H), 3.98 (m, 2 H), 4.60 (m, 1 H), 5.25 (m, 1 H), 7.17 (m, 10 H), 7.36–8.06 (m, 13 H), 8.46 (s, 1 H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 197.7 (C=O), 174.7, 172.0, 170.9, 169.8, 138.1, 136.4, 136.3, 135.6, 133.6, 132.7, 132.2, 130.7, 129.7, 129.3, 128.9, 128.7, 128.5, 128.4, 128.2, 128.15, 128.1, 127.6, 127.5, 126.7, 126.5, 125.9, 125.3, 125.0, 123.2, 122.8, 122.3, 65.6, 58.8, 54.2, 51.9, 44.5, 37.5, 37.0, 30.2, 27.9, 23.7, 22.2, 20.2, 18.4, 17.1; HRFAB calcd for $C_{53}H_{57}N_5O_5$ $(M)^+$ 843.4346, found $(M + H)^+$ 844.4424.

The yield of **37** was 23%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.50 (dd, 6 H), 1.18 (m, 3 H), 1.27–1.82 (m, 8 H), 2.20 (m, 1 H), 2.78 (m, 3 H), 2.98 (m, 3 H), 3.92 (m, 2 H), 4.46 (m, 2 H), 4.85 (m, 1 H), 7.08 (m, 15 H), 7.51 (m, 2 H), 7.82 (m, 4 H), 8.35 (s, 1 H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 172.3 (Q), 170.9 (Q), 169.9 (Q), 143.0 (Q), 136.8 (Q), 136.5 (Q), 135.7 (Q), 132.3 (Q), 129.8 (Q), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 126.0 (CH), 123.4 (CH), 65.5 (CH), 61.6 (CH_2), 59.0 (CH), 54.7 (CH), 54.3 (CH), 52.0 (CH_2), 48.7 (CH), 37.5 (CH_2), 37.1 (CH_2), 30.2 (CH), 27.4 (CH_2), 23.7 (CH_2), 22.3 (CH_2), 21.4 (CH_3), 18.7 (CH_3), 17.2 (CH_3); HRFAB calcd for $C_{49}H_{55}N_5O_5$ $(M)^+$ 793.4190, found $(M + H)^+$ 794.4243.

The yield of **38** was 39%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.50 (dd, 6 H), 0.78 (m, 2 H), 1.18–1.78 (m, 11 H), 2.14 (m, 1 H), 2.65 (m, 2 H), 2.79 (m, 2 H), 3.02 (dd, 1 H), 3.73 (s, 3 H), 3.88 (m, 1 H), 4.33 (m, 1 H), 4.53 (m, 1 H), 5.67 (m, 1 H), 7.07 (m, 10 H), 7.35 (m, 8 H), 7.64 (broad d, 1 H), 7.72 (broad d, 1 H), 7.95 (broad d, 1 H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 174.6, 172.0, 171.0, 169.9, 159.7, 138.2, 136.7, 136.6, 136.3, 133.7, 130.8, 129.5, 129.0, 128.8, 128.5, 128.3, 128.2, 127.7, 126.7, 126.6, 126.0, 125.4, 125.1, 123.0, 122.4, 120.4, 119.7, 112.5, 65.3, 59.0, 55.1, 54.3, 53.2, 51.9, 44.6, 37.5, 37.0, 30.2, 27.6, 23.6, 22.2, 20.4, 18.5, 17.2; HRFAB calcd for $C_{50}H_{57}N_5O_6$ $(M)^+$ 823.4295, found $(M + H)^+$ 824.4369.

The yield of **39** was 17%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.65 (dd, 6 H), 0.88 (m, 1 H), 1.30–2.30 (m, 12 H), 2.70–3.14 (m, 6 H), 3.83 (s, 3 H), 3.94 (m, 2 H), 4.52 (m, 2 H), 4.93 (m, 1 H), 7.07–7.48 (m, 19 H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 174.8 (Q), 172.1 (Q), 171.0 (Q), 169.9 (Q), 159.7 (Q), 142.9 (Q), 136.8 (Q), 136.4 (Q), 129.5 (CH), 128.9 (CH), 128.9 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 126.8 (CH), 126.7 (CH), 126.6 (CH), 125.9 (CH), 120.3 (CH), 119.7 (CH), 112.4 (CH), 65.2 (CH), 61.5 (CH_2), 58.9 (CH), 55.2 (OCH_3), 54.4 (CH), 54.2 (CH), 51.8 (CH_2), 48.6 (CH), 37.4 (CH_2), 37.0 (CH_2), 30.1 (CH), 27.3 (CH_2), 23.6 (CH_2), 22.2 (CH_2), 21.2 (CH_3), 18.6 (CH_3), 17.1 (CH_3); HRFAB calcd for $C_{46}H_{55}N_5O_6$ $(M)^+$ 773.4139, found $(M + H)^+$ 774.4245.

The yield of **40** was 6%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.64 (dd, 6 H), 0.78 (m, 1 H), 1.21–2.22 (m, 12 H), 2.63–3.12 (m, 6 H), 3.66–3.97 (m, 5 H), 4.49 (m, 1 H), 4.88 (m, 1 H), 6.97–7.47 (m, 19 H); HRFAB calcd for $C_{46}H_{55}N_5O_6$ $(M)^+$ 773.4139, found $(M + H)^+$ 774.4227.

The yield of **41** was 13%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.58–1.50 (m, 27 H), 1.79–2.28 (m, 3 H), 2.73–3.14 (m, 3 H), 3.36 (dd, 1 H), 3.78 (s, 3 H), 4.10 (m, 1 H), 4.62 (m, 3 H), 4.88 (m, 1 H), 7.04–7.43 (M, 19 H); HRFAB calcd for $C_{46}H_{54}N_4O_7$ $(M)^+$ 774.3979, found $(M + H)^+$ 775.4067.

The yield of **42** was 5%: ^1H NMR ($CDCl_3$–CD_3OD) δ 0.58 (dd, 6 H), 0.93–1.58 (m, 11 H), 2.20 (m, 1 H), 2.71–3.12 (m, 6 H), 3.92 (m, 2 H), 4.45 (m, 2 H), 4.87 (m, 1 H), 6.98–7.20 (m, 15 H), 7.52 (m, 2 H), 7.85 (m, 4 H), 8.38 (s, 1 H); HRFAB calcd for $C_{49}H_{55}N_5O_5$ $(M)^+$ 793.4190, found $(M + H)^+$ 794.4244.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds 1–56 (113 pages). Ordering information is given on any current masthead page.