Cyclopropane-Derived Peptidomimetics. Design, Synthesis, and Evaluation of Novel Enkephalin Analogues

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It is known that peptide mimics containing trans-substituted cyclopropanes stabilize extended conformations of oligopeptides, and molecular modeling studies now suggest that the corresponding *cis*-cyclopropane dipeptide isosteres could stabilize a reverse turn. To begin to assess this possibility, a series of cis-substituted cyclopropanes were incorporated as replacements of the Gly[2]-Gly[3] and Phe[4]-Leu[5] dipeptide subunits in Leu-enkephalin (H_2N-Tyr-Gly-Gly-Phe-Leu-OH), which is believed to bind to opiod receptors in a conformation containing a β-turn. General methods for the synthesis of the cyclopropane-containing dipeptide isosteres -XaaΨ[COcpCO]Yaa- and -XaaΨ[NHcpNH]Yaa- were developed by a sequence that featured the enantioselective cyclization of allylic diazoacetates catalyzed by the chiral rhodium complexes Rh_2[(5*S*)-MEPY]$_4$ and Rh_2[(5*R*)-MEPY]$_4$. A useful modification of the Weinreb amidation procedure was applied to the opening of the intermediate lactones with dipeptides, and a novel method for the synthesis of substituted diaminocyclopropanes was also developed. The Leu-enkephalin analogues were tested in a panel of binding and functional assays, and although those derivatives containing cyclopropane replacements of the Gly[2]-Gly[3] exhibited low micromolar affinity for the μ-receptor, analogues containing such replacements for the Phe[4]-Leu[5] subunit did not bind with significant affinity to any of the opiod receptors. These results are discussed.

Introduction

The ability to design small molecules that contain the key structural and functional elements of biologically active peptides is a central goal in drug discovery. However, a major challenge in this area is the ability to define the biologically active conformation, or the bound structure, of the peptide. Strategies for elucidating this structure typically involve introducing conformational restraints at specific sites of the peptide.[1] The solution structures of the constrained analogues can then be determined and correlated with binding and biological activity in an iterative process that ultimately provides insights regarding the bound conformation of the peptide. Most conformationally restricted replacements of peptide secondary structure imitate a turn or helix, but there have been several reports of mimics that enforce extended structures.[2] Most known peptide replacements have been designed only to constrain the backbone, and there are few that also are capable of orientating the amino acid side chains, which provide crucial sites for recognition, specificity, and binding. Thus, there is a need for peptide mimics that preorganize the peptide backbone and the side chains in the biologically active conformation of the native peptide.[3]

Toward identifying peptide replacements that would satisfy the above criteria and serve as useful tools to help elucidate the biologically active conformation of oligopeptides, we launched a program to evaluate the cyclopropanes **2** (-XaaΨ[COcpCO]Yaa-), and **3** (-XaaΨ[NHcpNH]-Yaa-) as novel mimics of the dipeptide **1**.[4−8] The cyclopropane ring in **2** incorporates the α-carbon, the nitrogen, and the β-carbon of the amino acid Yaa, whereas the cyclopropane in **3** replaces the α-carbon, the carbonyl carbon, and the β-carbon atom of Yaa. Preliminary molecular modeling studies to identify low-energy conformations of **2** and **3** indicated that when the backbone substituents were trans, the ϕ- or ψ-angle would be locked, and a local β-strand structure, a motif commonly

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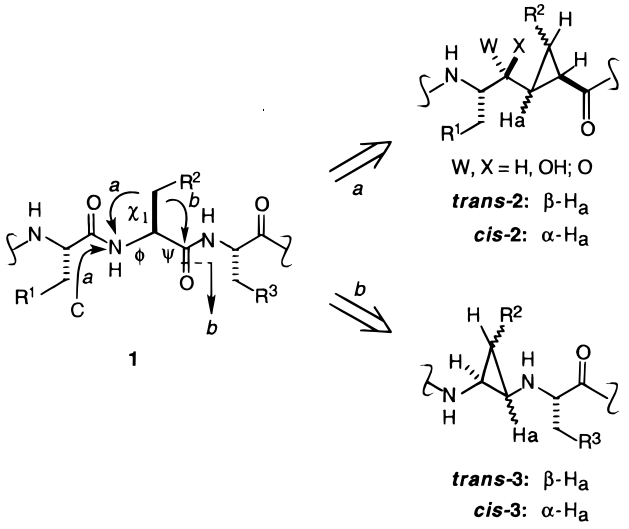
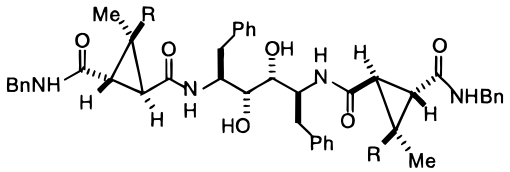
found in inhibitors bound to enzyme active sites,[9] would be preferred. Similar modeling studies of the isomers of **2** and **3** in which the backbone substituents were cis suggested that such replacements might enforce a reverse turn, such as a β-turn.[10] However, because of steric interactions between the side chains, extended structures were also observed as local minima. Depending upon the stereochemistry at the cyclopropyl carbons bearing R^2 in **2** and **3**, this side chain may occupy a spatial position *relative to the backbone* that approximates χ_1-angles in **1** of gauche(−) (−60°), gauche(+) (+60°), or anti (±180°).



As proof of the concept, we first introduced truncated analogues of ***trans*-2** into a number of potent pseudopeptide inhibitors of renin.[5] We have since incorporated replacements related to **2** and **3** in inhibitors of HIV-1 protease[6] and matrix metalloproteinases,[7,11] and others have used such cyclopropane-derived mimics in nonpeptide fibrinogen receptor antagonists.[12] We verified the predicted structural properties of peptide replacements related to **2** in our study of HIV-1 protease inhibitors wherein compounds **4** and **5**, which contain two cyclopropane replacements, were found to be subnanomolar inhibitors of HIV-1 protease that were equipotent with flexible analogues. The solution structure of **4** was determined by NMR, and the structure of the complex of **5** bound to HIV-1 protease was established by X-ray crystallography. Except at two terminal benzyl groups, the solution conformation of **4** was nearly identical to the enzyme-bound structures of **5** and other closely related, flexible HIV-1 protease inhibitors. Thus, the two cyclopropane rings in **4** and **5** stabilize extended structures in solution that correspond closely to the biologically active conformations of **4** and **5** as well as more flexible ligands.



The aforementioned studies established the underlying efficacy of cyclopropanes related to **2** and **3** as structural tools and isosteric mimics of dipeptide arrays in cases where the pseudopeptide is known to bind in an extended, β-strand conformation. However, we were interested in exploring the possibility that positioning the backbone substituents in a cis-orientation might locally stabilize a reverse turn. Inasmuch as enkephalins appear to bind to opiod receptors in a turned conformation (vide infra), it occurred to us that preparing and evaluating the biological activities of Leu-enkephalin analogues containing ***cis*-2** and ***cis*-3** mimics would present an opportunity to determine whether such replacements enforced their biologically active conformation. We now present the results of these investigations.

Results and Discussion

Design of Novel Enkephalin Analogues. Determining the three-dimensional structures of enkephalins, H_2N-Tyr-Gly-Gly-Phe-Leu(Met)-OH, bound to the μ- and δ-opioid receptors has been the focus of numerous investigations.[13,14] Conformationally constrained enkephalin derivatives have been identified that are highly potent and selective,[15] and an analysis of these and other reports suggests that a 5→2 β-turn might be an important structural motif in the biologically active conformation of these important neuropeptides.[16] On the basis of modeling studies, we reasoned that replacing the Gly^2-Gly^3 and the Phe^4-Leu^5 subunits with *cis*-GlyΨ[COcpCO]-

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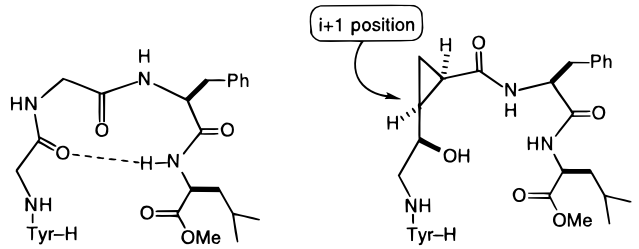
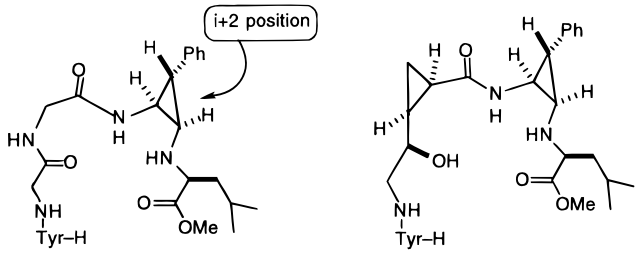
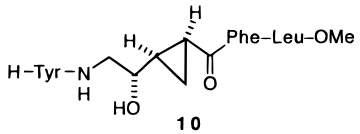
Ala- and *cis*-PheΨ[NHcpNH]Leu- isosteres, respectively, might stabilize such a reverse turn via geometric constraints alone. Consequently, the pseudopeptides **7**−**9**, which are analogues of Leu-enkephalin methyl ester (**6**), were selected as the primary targets for synthesis. Because it is likely that different conformations of Leu-enkephalin bind to the several types of opiod receptors, we postulated that altering the stereochemistry on the dipeptide replacement might eventuate in receptor selectivity. Pseudopeptides **10** and **11** were thus identified as additional targets for synthesis. The flexible analogues **12**−**14** were prepared as controls, as they are functionally more closely related to **7**−**11** than Leu-enkephalin itself.



6 **7**



8 **9**



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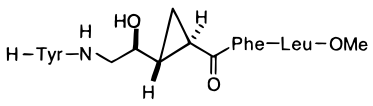
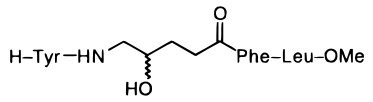
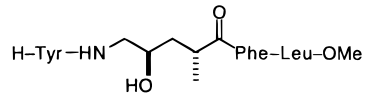


11



12: α-OH
13: β-OH



14

In the context of evaluating *cis*-cyclopropane replacements related to **2** and **3**, it is important to recognize that the enkephalin analogues **7**−**10** differ in some significant ways from Leu-enkephalin. Although each of these compounds contains geometric constraints that might stabilize a turned structure, they also lack one or more of the natural amide linkages that would presumably be involved in the intramolecular hydrogen bond between the Gly[2] and Leu[5] residues. Whether the loss of this hydrogen-bond would ultimately be detrimental to receptor binding affinity cannot be predicted a priori, because there are potent linear enkephalin analogues that cannot form hydrogen bond-stabilized 5→2 turns.[17] Thus, stabilization of the putative β-turn by an intramolecular hydrogen-bond is not itself essential for high-affinity binding to opiod receptors. Despite this argumentation, replacing the Gly[2]-Gly[3] amide bond was not without potential risk, as this linkage has been shown to play a role in determining enkephalin activity.[18] The orientation of phenyl group on the Phe[4] residue in χ-space was also known to be important as documented in studies involving enkephalins that contain dehydrophenylalanine[4] and cyclopropylphenylalanine[4] replacements.[19] Inasmuch as the phenyl group in **8** and **9** is constrained in an anti conformation, these enkephalin analogues might not be expected to bind strongly to the δ-receptor, where the gauche(−) orientation is known to be critical.[15b] On the other hand, compounds **8** and **9** might probe whether an anti orientation of the phenyl group was important for binding to other receptors.

Synthesis of Enkephalin Analogues. One of the significant challenges associated with the syntheses of pseudopeptides related to **7**−**11** was the design of a general entry to the dipeptide isosteres **2** and **3** that originated with non-amino acid precursors. To address this problem, we developed a stereoselective approach to cyclopropanes having the various substitution patterns found in **2** and **3** by a sequence of reactions that featured the enantioselective, intramolecular cyclopropanations of allylic diazoacetates, a construction that has been pioneered in our laboratories.[20,21] In the event, the synthesis of the enkephalin analogue **7** commenced with heating the diazo ester **15** in the presence of the chiral rhodium catalyst Rh_2[(5*S*)-MEPY]$_4$ to give **16** as the major product (≥94% ee; >95% de) (Scheme 1).[21] Ozonolysis of the double bond of **16** and reductive workup with sodium borohydride gave an intermediate alcohol that was converted in two steps (50% overall yield from **16**) into the azide **17**, which incorporates the essential functional and stereochemical features present in the cis-GlyΨ-[COcpCO]Ala- isostere.

The most direct tactic for elaborating the *C*-terminus of the pseudopeptide **7** would involve *N*-acylation of the H-Phe-Leu-OH dipeptide with the lactone **17**. However, at the outset of these investigations there were no known methods for achieving this useful transformation. We then discovered that cyclopropyl lactones related to **17** could be opened with amino acids and oligopeptides by a modification of the Weinreb amidation protocol,[7,22,23] and we recently extended this reaction to the preparation

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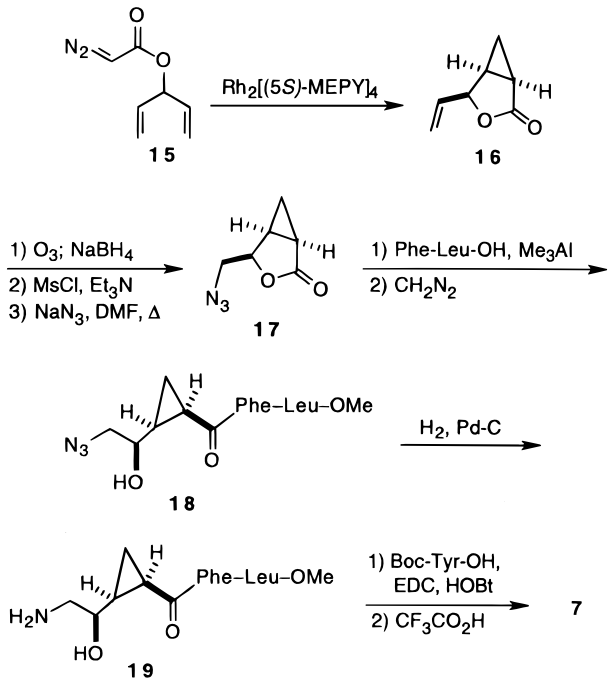
Scheme 1

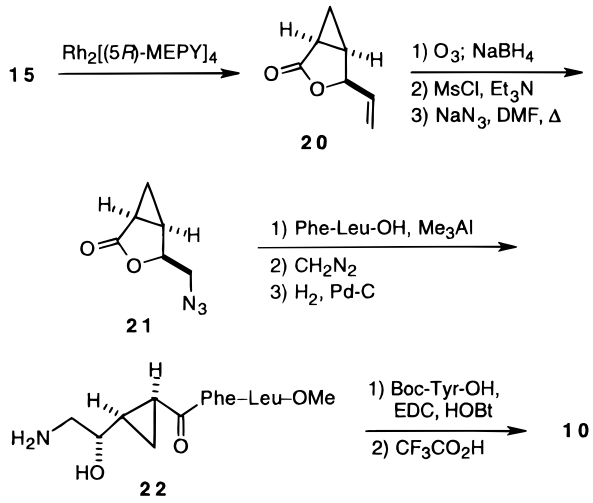


dipeptides.[24] Following this precedent, **17** was allowed to react with H-Phe-Leu-OH in the presence of Me_3Al (3 equiv) in refluxing dichloroethane followed by esterification of the intermediate acid with diazomethane to furnish **18** in 60% overall yield. Reduction of the azide function afforded **19**, which was transformed into the enkephalin analogue **7** in 67% yield by standard peptide coupling (HOBt, EDC) with Boc-Tyr-OH and acid-catalyzed deprotection. This route to **7** is both efficient and concise, requiring only 10 steps from commercially available starting materials.

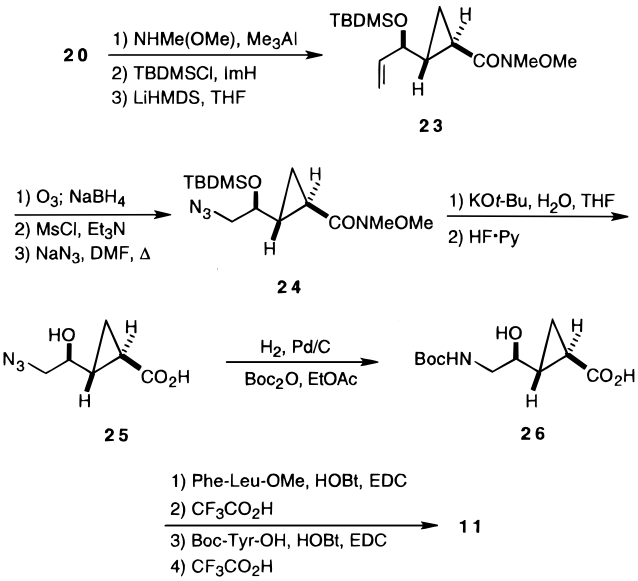
The diastereoisomeric enkephalin analogue **10**, in which the *cis*-GlyΨ[COcpCO]Ala- replacement is enantiomeric with that present in **7**, was prepared by a sequence of reactions identical to those shown in Scheme 1, except that $Rh_2[(5R)\text{-MEPY}]_4$ was used as the catalyst to effect enantioselective cyclization of **15** to give **20**, the enantiomer of **16** (Scheme 2).

The synthesis of the *trans*-GlyΨ[COcpCO]Ala- dipeptide replacement **26** required a stereochemical inversion at the *C*-terminal cyclopropyl carbon prior to its incorporation into **11** (Scheme 3). The lactone ring of the vinyl cyclopropane **20** was first opened by MeONHMe in the presence of Me_3Al, and after protection of the secondary hydroxyl group as a silyl ether, the stereocenter α to the hydroxamide group was epimerized using strong base to afford **23** in 48% yield overall yield from **20**. If the intermediate alcohol was not protected prior to epimerization, relactonization to return the starting lactone **20** was a significant side reaction. The subsequent transformation of **23** into the azide **24** proceeded in 60% overall yield following protocols previously developed for the syntheses of **17** and **21** (Schemes 1 and 2). Hydrolysis of the hydroxamide moiety in **24** followed by deprotection of the secondary hydroxyl group furnished **25**. The azide

Scheme 2



Scheme 3



was then reduced by catalytic hydrogenation in the presence of $(Boc)_2O$ to give the protected dipeptide isostere **26** in 63% overall yield from **24**. The final conversion of **26** into the enkephalin analogue **11** was achieved in 36% overall yield by sequential couplings with Phe-Leu-OMe and Boc-Tyr-OH according to standard protocols in peptide chemistry.

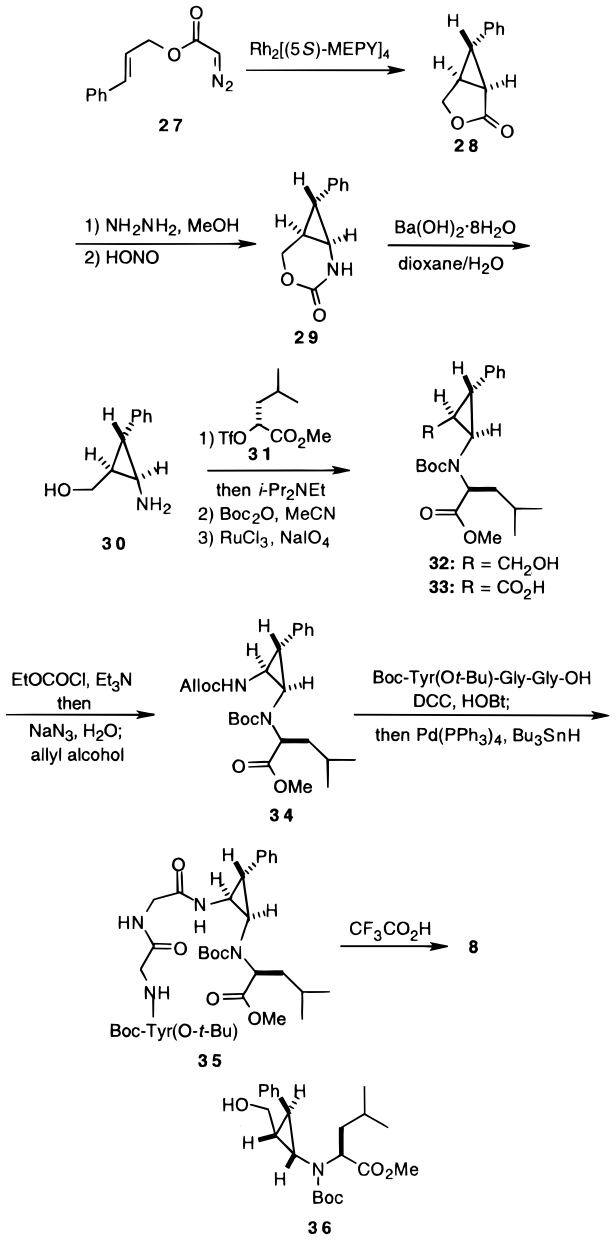
The syntheses of mimics of the general type **3** presented a somewhat greater challenge because of the known tendency of amino- and diaminocyclopropanes to undergo facile ring-opening reactions.[25] However, *N*-acylated aminocyclopropanes are much less inclined to suffer such deleterious side reactions. We were able to exploit the stabilizing effect derived from this *N*-acylation in the design of a novel approach to substituted diaminocyclopropanes as exemplified by the preparation of the protected *cis*-PheΨ[NHcpNH]Leu- isostere **34**, which was then incorporated in the enkephalin analogue **8** (Scheme 4).

(23) For an independent report of a related process, see: Hanko, R.; Rabe, K.; Dally, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1690−1693.

(24) Martin, S. F.; Dwyer, M. P.; Lynch, C. L. *Tetrahedron Lett.* **1998**, *39*, 1517−1520.

(25) For example, see: (a) Schroff, C. C.; Stewart, W. S.; Uhm, S. J.; Wheeler, J. W. *J. Org. Chem.* **1971**, *36*, 3356−3361. (b) Cannon, J. G.; Garst, J. E. *J. Org. Chem.* **1975**, *40*, 182−184. (c) Paulini, K.; Reissig, H.-R. *Liebigs Ann. Chem.* **1991**, 455−461. (d) Paulini, K.; Reissig, H.-U. *Liebigs Ann. Chem.* **1994**, 549−554. See also: (e) Von Der Saal, W.; Quast, H. *J. Org. Chem.* **1995**, *60*, 4024−4029.

Scheme 4



We had previously prepared the cyclopropyl lactone **28** by the Rh_2[(5*S*)-MEPY]$_4$-catalyzed cyclization of the diazo ester **27** in 77% yield and 65% ee,[20] and it was not necessary to increase the enantiomeric purity of **28**, as the unwanted enantiomer was easily removed at a later stage (vide infra). Thus, treatment of **28** with hydrazine followed by reaction of the resultant hydrazide with nitrous acid gave an intermediate hydroxy isocyanate that cyclized spontaneously to provide the urethane **29** in 83% overall yield. Base-induced hydrolysis of **29** then furnished the amino alcohol **30** (90% yield). The leucine fragment was then introduced by the *N*-alkylation of **30** with the triflate **31**, which was prepared from 5(*R*)-methyl oxopentanote[26] (Tf_2O, 2,6-lutidine, 25 min at 0 °C). The inseparable mixture (5:1) of secondary amines thus obtained was treated directly with Boc_2O to give a readily separable mixture of **32** (46% overall yield) together with its diastereoisomer **36** (9% overall yield).[27]

(26) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978−4984.

Oxidation of the primary alcohol in **32** with $RuCl_3/NaIO_4$ afforded the desired acid **33** (85% yield).[28]

When **33** was subjected to modified Curtius conditions using diphenyl phosphorazidate in the presence of allyl alcohol,[29] the carbamate **34** was produced, albeit in variable yields (40−75%), together with recovered starting material. However, **34** could be prepared in 85% yield from the acid **33** via a stepwise Curtius procedure that featured preparation of the intermediate azide by activation of the acid as a mixed anhydride.[30] The tactic that was invented for appending the *N*-terminal Tyr-Gly-Gly tripeptide moiety was inspired by an elegant transacylation procedure first developed by Hiemstra and Speckamp.[31] In a modification of this procedure, the Alloc carbamate **34** was allowed to react with the preformed HOBt ester of Boc-Tyr(O-*t*-Bu)-Gly-Gly-OH, which was generated in situ by the action of HOBt and DCC,[32] in the presence of $Pd(PPh_3)_4$ and Bu_3SnH to deliver **35** in 78% yield. Global deprotection of **35** with CF_3CO_2H then gave **8** in 90% yield.

The methods required for the synthesis of the biscyclopropane pseudopeptide **9** were now established, and two of the key intermediates **17** and **34** needed for this endeavor were already in hand. The lactone **17** was first converted into the ester **37** (70% yield) by acid-catalyzed methanolysis followed by protection of the secondary alcohol as its silyl ether (Scheme 5). Catalytic reduction of the azido group in **37** gave an intermediate amine that was coupled with a suitably protected tyrosine; subsequent hydrolysis of the *C*-terminal methyl ester afforded the acid **38** in 70% overall yield. The carboxylic acid in **38** was preactivated as its HOBt ester and allowed to react with **34** in the presence of $Pd(PPh_3)_4$ and Bu_3SnH according to our modified Hiemstra−Speckamp protocol to furnish **39** in 75% yield. Although the *tert*-butyl groups in **39** could not be cleanly removed under standard acidic conditions (CF_3COH/CH_2Cl_2, 4 N HCl/dioxane, etc.), treatment of **39** with excess trimethylsilyliodide in CH_3CN delivered **9** in 85% yield.[33]

It remained to prepare the flexible analogues **12**−**14** that would serve as controls in the biological evaluation of **7**−**11**. The synthesis of **12** commenced with opening the lactone ring of the known azide **40**[34] with the H-Phe-Leu-OH dipeptide in the presence of Me_3Al according to our modification of the Weinreb amidation;[7,24] esterification of the resulting acid with diazomethane then provided **41** in 63% yield (Scheme 6). Catalytic reduction of the azide functionality followed by coupling the intermediate amine with Boc-Tyr-OH and global deprotection

(27) For related reactions, see: (a) Chapman, K. T.; Kopka, I. E.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Izquierdo-Martin, M.; Niedzwiecki, L.; Chang, B.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Hagmann, W. K. *J. Med. Chem.* **1993**, *36*, 4293−4301. (b) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158−169.

(28) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. See also: (b) Godier-Marc, E.; Aitken, D. J.; Husson, H.-P. *Tetrahedron Lett.* **1997**, *38*, 4065−4068.

(29) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2157.

(30) Kaiser, C.; Weinstock, J. *Org. Synth.* **1988**, *6*, 910−913.

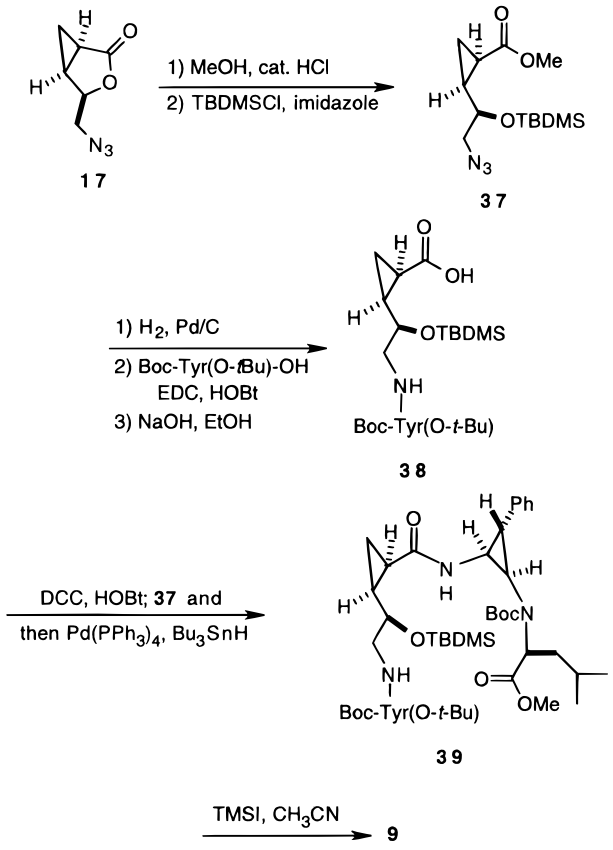
(31) Roos, E. C.; Bernabe, P.; Hiemstra, H, Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J. *J. Org. Chem.* **1995**, *60*, 1733−1740.

(32) Bower, J. D.; Guest, K. P.; Morgan, B. A. *J. Chem. Soc., Perkin 1* **1976**, 2488−2492.

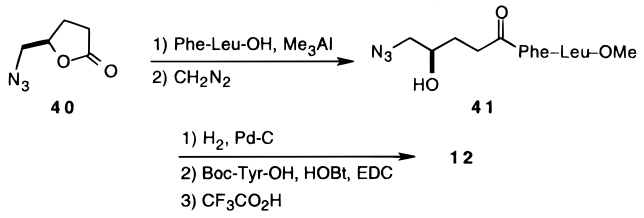
(33) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495−496.

(34) Olsen, R. K.; Bhat, K. L.; Wardle, R. B.; Hennen, W. J.; Kini, G. D. *J. Org. Chem.* **1985**, *50*, 896−899.

Scheme 5



Scheme 6



afforded **12** in 58% yield from **41**. The enantiomeric analogue **13** was synthesized in an identical fashion from the enantiomer of **40**, which was prepared from L-glutamic acid.

The synthesis of methyl analogue **14** was initiated by methylation of the known lactone **42**[35] to give a mixture (8:1) of diastereomers **43** and **44** in 75% overall yield (Scheme 7). When the enolate generated from this mixture was kinetically protonated, a new mixture (**43**:**44** = 1:6) was produced from which the desired cis isomer **44** was isolated as the major product (65% yield). Removal of the trityl group from **44** under acidic conditions followed by introduction of the azido function led to **45** in 59% overall yield. The subsequent transformation of **45** into **14** follows from the analogous sequence of reactions set forth in Scheme 6 for the preparation of **12**.

Biological Data for Enkephalin Mimetics. The cyclopropane-based enkephalin analogues **7**−**11** together with the flexible controls **12**−**14** and Leu-enkephalin methyl ester (**6**) were submitted to the National Institute for Drug Abuse (NIDA) for biological evaluation in a standard panel of receptor binding and functional assays.

(35) Takano, S.; Yonaga, M.; Ogasawara, K. *Synthesis* **1981**, 265−266.

Scheme 7

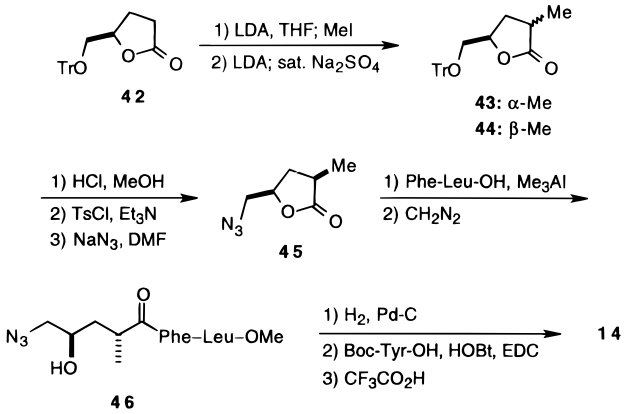


Table 1. Biological Activities of Constrained and Flexible Leu-enkephalin Analogues

	K_i, (nM)		IC_{50} (nM)	
compound	[^{3}H]DAMGO	[^{3}H]Cl-DPDPE	GPI(μ)	MVD(δ)
Leu-enkephalin	22	2	87	7
6	3.9 ± 1.1	10.6 ± 3.0	167 ± 14	87 ± 15
7	1355 ± 263	>10000	640 ± 241	4261 ± 921
8	>10000	>10000	NA[a]	NA
9	>10000	>10000	NA	NA
10	1344 ± 367	>10000	NA	NA
11	2159 ± 95	>10000	NA	NA
12	1367 ± 111	>10000	NA	NA
13	1194 ± 539	>10000	NA	NA
14	438 ± 230	>10000	NA	NA

[a] NA = not active up to 10000 nM.

The binding affinities, which were calculated as K_is,[36] of these compounds to the μ- and δ-opiate receptors were determined by their ability to displace the radioligands [^{3}H]DAMGO and [^{3}H]Cl-DPDPE, respectively, from crude guinea pig brain membranes; concentrations of the test compounds were varied from 10^{-5} to 10^{-10} nM. The opiate agonist potentials of the test compounds were then determined using electrically stimulated guinea pig ileum (GPI) and mouse vas deferens (MVD) muscle preparations.[37−39] The tissues were stimulated and treated with the test compounds, and the inhibition of the muscle contraction was measured at different concentrations to obtain a concentration−response curve. The IC_{50} in these assays was defined as the concentration of the agonist that caused 50% inhibition of the electrically induced contractions. The results obtained for the radioligand binding assays as well as the GPI and MVD bioassays are summarized in Table 1.

As measured by their K_is, the cyclopropane-containing pseudopeptides **7**, **10**, and **11** as well as the flexible controls **12**−**14** exhibited low micromolar binding affinity for the μ-receptor and virtually no affinity for the δ-receptor, whereas the cyclopropane-containing pseudopeptides **8** and **9** had no observable affinity for either opioid receptor. In the functional assays, only **7** exhibited weak agonist activity for the μ- and δ-receptors as measured by the experimental IC_{50}s. The ratio of the IC_{50}

(36) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

(37) Paton, W. D. M.; Vizi, E. S. *Br. J. Pharmacol.* **1969**, *35*, 10−29.

(38) Hughes, J.; Kosterlitz, H. W.; Leslie, F. M. *Br. J. Pharmcol.* **1975**, *53*, 371−381.

(39) Ronai, A. Z.; Graf, L.; Szekely, J. I.; Dunai-Kovacs, Z.; Bajusz, S. *FEBS Lett.* **1977**, *74*, 182−184.

values obtained for opiate agonists in the GPI and MVD assays is a common indicator of μ- or δ-receptor selectivity, and the ratio for IC_{50}(MVD)/IC_{50}(GPI) of 6.7 for **7** shows a reasonable preference for the μ-receptor. Interestingly, the methyl ester of Leu-enkephalin (**6**) exhibited the opposite selectivity and with a slight preference for the δ-receptor.

The weak μ-receptor binding and the lack of δ-receptor binding of the constrained Leu-enkephalin analogues **7**−**11** suggest that these molecules do not embody those structural features that are important for binding to the μ- and δ-opioid receptors. We were aware of the risks associated with replacing the enkephalin Gly^2-Gly^3 dipeptide with the -GlyΨ[COcpCO]Ala- isostere in **7**, **10**, and **11**, because it had been previously shown that the amide bond between Gly^2 and Gly^3 was important for biological activity.[18] Other substitutions of the Gly^2-Gly^3 dipeptide have also yielded relatively inactive compounds.[40] Thus, the comparable biological activities of **7**, **10** and **11** and the flexible controls **12**−**14** further demonstrate that there is little tolerance for significant structural and functional modifications of the Gly^2-Gly^3 amide.

Although pseudopeptides bearing Gly^2-Gly^3 replacements retained some affinity for the μ-receptor, analogues **8** and **9**, which contain the *cis*-PheΨ[NHcpNH]Leu- replacement for the Phe^4-Leu^5 dipeptide, displayed no measurable binding affinity for either the μ- or the δ-opioid receptors. The orientation of the phenyl group at Phe^4 is known to be important for binding to these receptors.[19] For example, a gauche(−) orientation of Phe^4 appears to be required for optimal interaction with the δ-opiod receptor.[15b] Thus, one plausible explanation for the observed lack of activity of **8** and **9** is that the phenyl group in these pseudopeptides, which is fixed in an anti conformation in χ_1-space, is not properly oriented for interaction with the receptor. Other factors contributing to the lack of activity could be the basic nature of the aminocyclopropyl moiety ($pK_a = 9.1$)[41] in **8** and **9** and/or the loss of the Leu^5 amide N−H that helps stabilize a β-turn via an intramolecular hydrogen bond. In this latter context, however, it should be noted that there are replacements of the Phe^4-Leu/Met^5 amide bond that give enkephalin analogues having potencies comparable to those of the appropriate reference compounds.[42]

Conclusions

A series of conformationally constrained analogues of Leu-enkephalin that contain the novel cyclopropane dipeptide mimics **2** (-GlyΨ[COcpCO]Ala-) and **3** (-PheΨ-[NHcpNH]Leu-) were prepared and evaluated for biological activity. A number of concise and efficient protocols were developed for the enantioselective syntheses of these dipeptide isosteres, and these methods may be applied to the preparation of rigid analogues of other pseudopeptides. For example, an effective technique for opening lactones directly with dipeptides in the presence of $AlMe_3$ was developed, and tactics for preparing substituted diaminocyclopropanes were discovered. These studies show that the *cis*-GlyΨ[COcpCO]Ala- and *cis*-PheΨ-[NHcpNH]Leu- replacements that were introduced in the pseudopeptides **7**−**11** do not adequately mimic the requisite structural and functional features at the Gly^2-Gly^3 and the Phe^4-Leu^5 subsites in any of the biologically active conformations of Leu-enkephalin at opiod receptors. Although the Gly^2-Gly^3 linkage and the orientation of the phenyl group are clearly important, it is premature to make further conclusions regarding the significance of these experiments because structural information regarding what geometric constraints are imposed by the *cis*-GlyΨ[COcpCO]Ala- and *cis*-PheΨ[NHcpNH]Leu- replacements is presently lacking. Preliminary NMR work shows there is some local order about the cyclopropane rings in **7**−**11**, but the remaining sections of the molecules are flexible with no apparent ordered structure. NMR studies to establish the solution structures of pseudopeptides containing the dipeptide isosteres **2** and **3** and additional studies in which these novel replacements are incorporated in other biologically active peptides are in progress, and the results of these investigations will be reported in due course.

Experimental Section

General. Unless otherwise noted, solvents and reagents were reagent grade and used without purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone ketyl under nitrogen, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been oven- or flame-dried. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; and comp, complex multiplet. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM). Percent yields are given for compounds that were ≥95% pure as judged by NMR.

General Procedure for Preparing Allylic Diazoacetates. The *p*-toluenesulfonyl hydrazone of glyoxylic chloride was added to a solution of the alcohol in dry CH_2Cl_2 (0.20 M) at 0 °C, whereupon *N*,*N*-dimethylaniline (1.10 equiv) was added. After the mixture was stirred at 0 °C for 15 min, Et_3N (5.13 equiv) was added slowly. The resulting dark suspension was stirred for 15 min at 0 °C and then for 30 min at room temperature, whereupon an equal volume of water was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 1 volume), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude diazoester thus obtained was purified by flash chromatography using either hexane/EtOAc or pentane/Et_2O mixtures (ratios given) to furnish pure allylic diazoacetates as yellow oils.

1,4-Pentadienyl-3-diazoacetate (15). The crude product was purified by flash chromatography eluting with pentane/Et_2O (20:1) to provide 1.19 g (65%) of a yellow liquid: ^1H NMR ($CDCl_3$) δ 5.91−5.78 (comp, 3 H), 5.34−5.23 (comp, 4 H), 4.79 (s, 1 H); ^{13}C NMR δ 165.8, 134.9, 117.5, 75.3, 46.3; IR ($CHCl_3$) ν 2116, 1692 cm^{-1}.

(40) (a) Belanger, P. C.; Dufresne, C.; Scheigetz, J.; Young, R. N.; Springer, J. P.; Dmitrienko, G. I. *Can J. Chem.* **1982**, *60*, 1019−1029. (b) Belanger, P. C.; Dufresne, C. *Can. J. Chem.* **1986**, *64*, 1514−1520. (c) Claridge, T. D. W.; Hulme, C.; Kelly, R. J.; Lee, V.; Nash, I. A.; Schofield, C. J. *Biorg. Med. Chem. Lett.* **1996**, *6*, 485−490. (d) von Roedern, E. G.; Lohof, E.; Hessler, G.; Hoffman, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156−10167.

(41) Christensen, J. J.; Izatt, R. M.; Wrathall, D. P.; Hansen, L. D. *J. Chem. Soc. (A)* **1969**, 1212−1223.

(42) Morley, J. S.; Dutta, A. S. Structure-Activity Relationships of Opiod Peptides. In *Opioid Peptides: Medicinal Chemistry*; NIDA Monograph 69; Rapaka, R. S.; Barnett, G.; Hawks, R. L., Eds., 1986; p 42−64.

General Procedure for the Cyclization of Diazoacetates in the Presence of Rh_2[(5*S*)-MEPY]$_4$ and Rh_2[(5*R*)-MEPY]$_4$. A solution of the diazo ester in dry CH_2Cl_2 (0.010 M) was added via syringe pump to a refluxing solution of the chiral rhodium catalyst in CH_2Cl_2 (0.01 equiv, 1×10^{-4} M) over a period of 12−18 h. The reaction was cooled to room temperature, and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography eluting with pentane/ether (ratios given).

[1*S*-(1α,4α,5α)]-4-Vinyl-3-oxabicyclo[3.1.0]hexan-2-one (16) was prepared in 90% yield from **15** and Rh_2[(5*S*)-MEPY]$_4$. The crude cyclopropane was purified by flash chromatography eluting with pentane/ether (1:1). The enantiomeric excess had previously been determined to be ≥94%:[26] ^{1}H NMR (300 MHz) δ 5.79−5.68 (m, 1 H), 5.29−5.16 (comp, 2 H), 4.95 (t, J = 5.1 Hz, 1 H), 2.25−2.18 (m, 1 H), 2.03−1.97 (m, 1 H), 1.08−1.01 (m, 1 H), 0.82−0.78 (m, 1 H); ^{13}C NMR (75 MHz) δ 175.2, 132.6, 117.6, 78.7, 20.6, 17.9, 8.7; IR (neat) ν 1770 cm^{-1}; mass spectrum (CI) m/z 125.0605 ($C_7H_8O_2$ + H requires 125.0602).

[1*S*-(1α,4α,5α)]-4-Hydroxymethyl-3-oxabicyclo[3.1.0]-hexan-2-one. Ozone was passed through a solution of **16** (0.57 g, 4.6 mmol) in MeOH/CH_2Cl_2 (3:1, 40 mL) at −78 °C until the solution was blue. The excess ozone was removed by purging with argon, whereupon $NaBH_4$ (0.34 g, 9.2 mmol) was added and the reaction stirred for 10 min at −78 °C. The mixture was warmed to 0 °C and stirred for 30 min, and saturated aqueous NH_4Cl (10 mL) then was slowly added. The volatiles were removed under reduced pressure, and the resulting aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed brine (1 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude residue was purified by flash chromatography using hexanes/EtOAc (1:3) to afford 353 mg (60%) of the alcohol as a pale yellow oil: ^{1}H NMR (300 MHz) δ 4.76−4.69 (m, 1 H), 3.81−3.69 (m, 2 H), 3.58 (s, 1H), 2.30−2.22 (m, 1 H), 2.14−2.08 (m, 1 H), 1.19−1.12 (m, 1 H), 1.08−1.04 (m, 1 H); ^{13}C NMR (75 MHz) δ 176.0, 79.5, 62.2, 18.6, 17.3, 8.6; IR ($CHCl_3$) ν 1770 cm^{-1}; mass spectrum (CI) m/z 129.0549 ($C_6H_8O_3$ + H requires 129.0552), 111 (base).

[1*S*-(1α,4α,5α)]-4-Methanesulfonylmethyl-3-oxabicyclo-[3.1.0]hexan-2-one. A solution of alcohol from the preceding experiment (0.10 g, 0.78 mmol) in CH_2Cl_2 (4 mL), Et_3N (0.16 mL, 1.2 mmol), and methanesulfonyl chloride (0.07 mL, 0.94 mmol) was stirred for 1 h at 0 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 10% aqueous HCl (1 × 10 mL) and brine (1 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:3) to afford 0.11 g (90%) of the mesylate as a pale yellow oil: ^{1}H NMR (300 MHz) δ 4.89−4.84 (m, 1 H), 4.38 (dd, J = 4.3, 11.2 Hz, 1 H), 4.27 (dd, J = 7.0, 11.2 Hz, 1 H), 3.07 (s, 3 H), 2.34−2.28 (m, 1 H), 2.22−2.16 (m, 1 H), 1.28−1.21 (m, 1 H), 1.05 (dd, J = 4.7, 8.3 Hz, 1 H); ^{13}C NMR (75 MHz) δ 174.5, 75.5, 68.4, 37.6, 18.2, 17.4, 8.8; IR ($CHCl_3$) ν 1784, 1550 cm^{-1}; mass spectrum (CI) m/z 207.0332 ($C_7H_{10}O_5S$ + H requires 207.0327).

[1*S*-(1α,4α,5α)]-4-Azidomethyl-3-oxabicyclo[3.1.0]hexan-2-one (17). A mixture of the mesylate from the preceding experiment (0.14 g, 0.67 mmol) and NaN_3 (0.44 g, 6.7 mmol) in DMF (3 mL) was heated at 65 °C for 12 h. After cooling to room temperature, Et_2O (20 mL) was added, and the solution was washed with water (2 × 7 mL) and brine (1 × 7 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to yield 0.15 g (90%) of **17** as a yellow oil: ^{1}H NMR (300 MHz) δ 4.66 (dd, J = 5.3, 6.5 Hz, 1 H), 3.50−3.40 (m, 2 H), 2.28−2.21 (m, 1 H), 2.15−2.09 (m, 1 H), 1.18−1.13 (m, 1 H), 1.02−0.98 (m, 1 H); ^{13}C NMR (75 MHz) δ 174.6, 76.8, 51.8, 19.1, 17.6, 8.7; IR ($CHCl_3$) ν 2109, 1778 cm^{-1}; mass spectrum (CI) m/z 154.0612 ($C_6H_7N_3O_2$ + H requires 154.0617) (base).

General Procedure for Opening Cyclopropyl Lactones with Phe-Leu-OH. A solution of Me_3Al in hexanes (2.0 M, 9 equiv) was added to a suspension of Phe-Leu-OH (3 equiv) in CH_2ClCH_2Cl (0.24 M) at room temperature over 40 min, and the resulting solution was stirred at room temperature for 45 min. A solution of the appropriate cyclopropyl lactone **17**, **21**, **40**, or **45** (1 equiv) in CH_2ClCH_2Cl (0.12 M) was then added dropwise over 20 min, and the reaction was heated at reflux for 24 h. After cooling to 0 °C, 1 N HCl (2 vol) was carefully added, and the mixture was extracted with CH_2Cl_2 (3 × 1 volume). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude pseudotetrapeptides were purified by flash chromatography using CH_2Cl_2/MeOH mixtures (ratio given) as eluant to afford the pseudopeptide acids.

***N*-[(1*S*-(1α,2α,1′α))-2-(2′-Azido)ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine** was prepared in 60% yield from **17** as a waxy white solid: CH_2Cl_2/MeOH (15:1); mp 146−148 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.20 (comp, 5 H), 4.75−4.69 (m, 1 H), 4.43−4.39 (m, 1 H), 3.52 (dt, J = 4.7, 9.1 Hz, 1 H), 3.20 (dd, J = 4.3, 14.1 Hz, 1 H), 2.80 (dd, J = 11.1, 14.4 Hz, 1 H), 2.54 (d, J = 4.9 Hz, 2 H), 1.62−1.70 (comp, 4 H), 1.18−1.15 (m, 1 H), 1.07−1.01 (m, 1 H), 0.99−0.96 (m, 1 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.92 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.9, 174.0, 173.4, 138.4, 130.3, 129.5, 127.7, 70.1, 57.1, 55.8, 52.2, 41.7, 39.0, 25.9, 24.3, 23.4, 21.9, 20.1, 11.6; IR (Nujol) ν 3440, 3282, 2100, 1713, 1638, 1560 cm^{-1}; mass spectrum (CI) m/z 432.2232 ($C_{21}H_{29}N_5O_5$ + H requires 432.2247).

General Procedure for Esterification of Carbocyclic Acids with Diazomethane. An ethereal solution of CH_2N_2 was added to a solution of the carboxylic acid derivative until a bright yellow color persisted. The excess CH_2N_2 was removed by bubbling argon through the reaction mixture and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography using MeOH/CH_2Cl_2 mixtures (ratio given) as the eluant to afford the corresponding methyl esters.

***N*-[(1*S*-(1α,2α,1′α))-2-(2′-Azido)ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester (18)** was prepared in 95% yield from the corresponding acid as a clear glassy solid: MeOH/CH_2Cl_2 (25:1); mp 115−117 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.21 (comp, 5 H), 4.75 (dd, J = 4.4, 10.7 Hz, 1 H), 4.50−4.45 (m, 1 H), 3.69 (s, 3 H), 3.53 (dt, J = 4.5, 9.9 Hz, 1 H), 3.17 (dd, J = 4.4, 14.0 Hz, 1 H), 2.81 (dd, J = 10.5, 14.0 Hz, 1 H), 2.57 (d, J = 4.9 Hz, 2 H), 1.73−1.59 (comp, 4 H), 1.18−1.12 (m, 1 H), 1.08−1.01 (m, 1 H), 0.99−0.96 (m, 1 H), 0.94 (d, J = 6.2 Hz, 3 H), 0.90 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.4, 174.0, 173.3, 138.6, 130.3, 129.5, 127.7, 70.0, 57.2, 55.7, 52.7, 52.2, 41.5, 39.0, 25.9, 24.4, 23.2, 21.9, 20.1, 11.5; IR ($CHCl_3$) ν 3292, 2108, 1675, 1639, 1555 cm^{-1}; mass spectrum (CI) m/z 446.2401 ($C_{22}H_{31}N_5O_5$ + H requires 446.2403).

General Procedure for Reduction of Azides. A mixture of azide (1 equiv) in MeOH (0.3 M) containing 10% Pd/C (cat.) was stirred under H_2 (1 atm) for 6−8 h. The reaction mixture was filtered through a Celite pad, and the pad was washed with MeOH (3 volumes). The combined filtrates were concentrated under reduced pressure, and the crude amines were used without further purification.

***N*-[(1*S*-(1α,2α,1′α))-2-(2′-Amino)ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester (19)** was prepared in 90% yield from **18** as a pale yellow solid: mp 90−93 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.20 (comp, 5H), 4.74−4.69 (m, 1 H), 4.48−4.43 (m, 1 H), 3.68 (s, 3 H), 3.37−3.33 (m, 1 H), 3.14 (dd, J = 5.0, 14.0 Hz, 1 H), 2.84 (dd, J = 10.1, 14.0 Hz, 1 H), 2.25 (dd, J = 8.0, 13.2 Hz, 1 H), 2.15 (dd, J = 3.7, 13.2 Hz, 1 H), 1.74−1.58 (comp, 4 H), 1.10−1.06 (comp, 2 H), 1.00−0.97 (m, 1 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.4, 174.0, 173.9, 138.6, 130.3, 129.5, 127.8, 71.5, 55.8, 52.7, 52.2, 49.3, 41.5, 39.0, 25.9, 25.2, 23.3, 21.9, 20.1, 11.1; IR (Nujol) ν 3298, 1744, 1636, 1560 cm^{-1}; mass spectrum (CI) m/z 420.2495 ($C_{22}H_{33}N_2O_5$ + H requires 420.2498), 212 (base).

General Procedure for Coupling Pseudotetrapeptides with Boc-Tyr-OH. To a solution of pseudotetrapeptide (1 equiv) in dry DMF (0.07 M) at 0 °C were added HOBt (3.2 equiv), Boc-Tyr-OH (1.2 equiv), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (1.2 equiv). The mixture was allowed to warm to room temperature and stir for 14 h. The solution was partitioned between EtOAc (2 volumes) and brine (1 volume), and the aqueous layer was extracted with EtOAc (2 × 2 volumes). The combined organic layers were washed with 10% citric acid (2 × 1 volume), saturated aqueous $NaHCO_3$ (2 × 1 volume), and brine (2 × 1 volume). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by flash chromatography using CH_2Cl_2/MeOH mixtures (ratio given) as eluant to afford the desired pseudopentapeptides.

***N*-[(1*S*-(1α,2α,1′α))-2-[2′-(*N*-(*tert*-Butoxycarbonyl)-L-tyrosine)amino]ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester** was prepared in 73% yield from **19** as a white solid: CH_2Cl_2/MeOH (25:1); mp 130−132 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.15 (comp, 5 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 4.74−4.71 (m, 1 H), 4.47−4.45 (m, 1 H), 4.23−4.18 (m, 1 H), 3.67 (s, 3 H) 3.48−3.32 (m, 1 H), 3.16 (dd, *J* = 5.6, 14.0 Hz, 1 H), 3.00 (dd, *J* = 5.8, 13.9 Hz, 2 H), 2.89 (dd, *J* = 9.4, 13.9 Hz, 1 H), 2.70−2.56 (m, 2 H), 1.70−1.56 (comp, 4 H), 1.36 (s, 9 H), 1.30−1.21 (m, 1 H), 1.19−0.97 (comp, 2 H), 0.93 (d, *J* = 6.3 Hz, 3 H), 0.90 (d, *J* = 6.3 Hz, 3 H)); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4, 174.5, 174.3, 173.8, 157.6, 157.2, 138.4, 131.4, 130.3, 129.5, 129.3, 127.4, 116.2, 80.7, 69.5, 57.8, 55.8, 52.7, 52.2, 45.9, 41.5, 38.9, 38.5, 28.7, 25.9, 24.7, 23.3, 21.9, 20.3, 11.0; IR ($CHCl_3$) ν 2995, 1735, 1685 cm^{-1}; mass spectrum (CI) *m*/*z* 683.3640 ($C_{36}H_{50}N_4O_9$ + H requires 683.3656), 293 (base).

***N*-[(1*S*-(1α,2β,1′β))-2-[2′-(*N*-(*tert*-Butoxycarbonyl)-L-tyrosine)amino]ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester** was prepared by the general coupling procedure in 68% yield from the corresponding pseudotetrapeptide as an off-white solid: CH_2Cl_2/MeOH (25:1); mp 105−107 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.25−7.16 (comp, 5 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 4.64 (dd, *J* = 5.3, 8.9 Hz, 1 H), 4.45 (dd, *J* = 5.7, 8.8 Hz, 1 H), 4.21−4.16 (m, 1 H), 3.68 (s, 3 H), 3.34−3.30 (m, 1 H), 3.19−3.14 (comp, 2 H), 3.01−2.84 (comp, 3 H), 2.77−2.63 (m, 1 H), 1.66−1.53 (comp, 4 H), 1.37 (s, 9 H), 1.19−1.03 (m, 1 H), 1.01−0.98 (m, 1 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 0.90−0.85 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 174.7, 174.4, 173.7, 157.7, 157.3, 138.5, 131.4, 130.5, 129.4, 129.3, 127.7, 116.3, 81.0, 72.8, 57.9, 55.8, 52.7, 52.2, 46.6, 41.5, 39.0, 38.5, 28.7, 25.9, 25.6, 23.3, 21.9, 19.6, 11.6; IR ($CHCl_3$) ν 3398, 2956, 1739, 1666 cm^{-1}; mass spectrum (CI) *m*/*z* 683.3663 ($C_{36}H_{50}N_4O_9$ + H requires 683.3656), 261 (base).

[1*R*-(1α,2α,1′α)]-(*N*-methoxy-*N*-methyl)-2-(2′-propen-1′-ol)cyclopropane-1-carboxamide. A solution of $AlMe_3$ (19 mL of a 2.0 M solution in hexanes, 38.0 mmol) was added dropwise over the course of 20 min to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.8 g, 29 mmol) in CH_2Cl_2 (120 mL) at room temperature, and the resulting homogeneous solution was stirred at room temperature for 30 min. A solution of **20** (1.2 g, 9.7 mmol) in CH_2Cl_2 (80 mL) was then added dropwise, and the mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0 °C, and 10% aqueous HCl (100 mL) was slowly added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with hexane/EtOAc (1:2) to afford 1.5 g (84%) of the amide/alcohol as a pale yellow oil: ^{1}H NMR (300 MHz) δ 5.84−5.73 (m, 1 H), 5.08 (d, *J* = 17.1 Hz, 1 H), 4.95 (d, *J* = 10.3 Hz, 1 H), 4.07 (t, *J* = 6.3 Hz, 1 H), 3.63 (s, 3 H), 3.09 (s, 3 H), 2.20 (br s, 1 H), 1.39−1.29 (comp, 2 H), 1.03−0.97 (m, 1 H); ^{13}C NMR (75 MHz) δ 171.5, 139.9, 113.4, 69.7, 61.0, 32.0, 26.4, 14.9, 10.3; IR (neat) ν 3425, 2980, 1640 cm^{-1}; mass spectrum (CI) *m*/*z* 186.1131 ($C_9H_{15}NO_3$ + H requires 186.1130), 168 (base).

[1*R*-(1α,2α,1′α)]-2-[1′-(*tert*-Butyldimethylsiloxy)-2′-propenyl]cyclopropane-1-*N*-methoxy-*N*-methyl-carboxamide. A solution of the alcohol from the previous experiment (1.4 g, 7.6 mmol) in DMF (25 mL) containing imidazole (1.3 g, 19 mmol) and *tert*-butyldimethylsilyl chloride (1.7 g, 11 mmol) was stirred for 12 h at room temperature, whereupon H_2O (15 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the organic layers were combined and washed with 10% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine (2 × 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to afford 2.1 g (93%) of the protected material as a pale yellow oil: ^{1}H NMR (300 MHz) δ 5.84−5.73 (m, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 4.94 (d, *J* = 10.3 Hz, 1 H), 3.70 (s, 3 H), 3.17 (s, 3 H), 2.30−2.20 (br s, 1 H), 1.44−1.24 (comp, 2 H), 1.11−1.01 (m, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz) δ 172.5, 141.0, 113.0, 72.1, 61.5, 32.6, 26.4, 25.8, 18.1, 15.5, 12.1, −4.4, −4.6; IR (neat) ν 2960, 1660 cm^{-1}; mass spectrum (CI) *m*/*z* 300.1995 ($C_{15}H_{30}NO_3Si$ + H requires 300.1995), 242 (base).

[1*S*-(1α,2β,1′β)]-2-[1′-(*tert*-Butyldimethylsiloxy)]-2′-propenylcyclopropane-1-*N*-methoxy-*N*-methylcarboxamide (23). A solution of sodium bis(trimethysilyl)amide in THF (21 mL of a 1 M solution in THF, 21 mmol) was added dropwise to a solution of the protected alcohol from the previous experiment (2.0 g, 7.0 mmol) in THF (50 mL) at 0 °C. After stirring for 4 h at 0 °C, saturated aqueous NH_4Cl (35 mL) was added, and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic fractions were washed with 10% aqueous HCl (2 × 60 mL) and brine (2 × 60 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to afford 1.3 g (62%) of **23** as a pale yellow oil: ^{1}H NMR (300 MHz) δ 5.83−5.74 (m, 1 H), 5.16 (d, *J* = 17.1 Hz, 1 H), 5.05 (d, *J* = 10.3 Hz, 1 H), 4.13 (t, *J* = 5.0 Hz, 1 H), 3.72 (s, 3 H), 3.18 (s, 3 H,), 2.16−2.14 (br s, 1 H), 1.59−1.51 (m, 1 H), 1.13−1.07 (m, 1 H), 0.98−0.91 (m, 1 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz) δ 174.0, 140.1, 114.3, 72.3, 61.4, 32.4, 27.4, 25.6, 18.1, 13.7, 10.5, −4.4, −5.0; IR (neat) ν 2960, 1660 cm^{-1}; mass spectrum (CI) *m*/*z* 300.1986 ($C_{15}H_{29}NO_3Si$ + H requires 300.1995), 242 (base).

[1*S*-(1α,2β,1′β)]-2-[1′-(*tert*-Butyldimethylsiloxy)]ethan-2′-ol-cyclopropane-1-*N*-methoxy-*N*-methylcarboxamide. Ozone was bubbled through a solution of **23** (1.3 g, 4.4 mmol) in MeOH/CH_2Cl_2 (3:1, 300 mL) at −78 °C until a blue endpoint was reached, whereupon the excess ozone was removed with a stream of argon. After $NaBH_4$ (1.7 g, 44 mmol) was added, the reaction mixture was warmed to 0 °C and stirred for 1.5 h. Saturated aqueous NH_4Cl (150 mL) was added, and the mixture was concentrated under reduced pressure to approximately 30 mL. The aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were washed with 10% aqueous HCl (1 × 60 mL) and brine (1 × 60 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to afford 1.1 g (80%) of the alcohol as a pale yellow oil: ^{1}H NMR (300 MHz) δ 3.74 (s, 3 H), 3.63−3.50 (comp, 3 H), 3.19 (s, 3 H), 2.85−2.64 (br s, 1 H), 2.22−2.14 (m, 1 H), 1.62−1.5⁰ (m, 1 H), 1.16−1.08 (m, 1 H), 1.01−0.88 (m, 1 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); 13C NMR (75 MHz) δ 173.8, 72.9, 66.8, 61.5, 32.5, 25.7, 24.3, 18.0, 13.8, 11.3, −4.5, −4.7; IR (neat) ν 3440, 2960, 1730, 1630 cm^{-1}; mass spectrum (CI) *m*/*z* 304.1942 ($C_{14}H_{30}NO_4Si$ + H requires 304.1944), 172 (base).

[1*S*-(1α,2β,1′β)]-2-[1′-(*tert*-Butyldimethylsiloxy)-2′-methanesulfonyl]ethylcyclopropane-1-*N*-methoxy-*N*-methylcarboxamide. A solution of alcohol (1.1 g, 3.6 mmol) in CH_2Cl_2 (25 mL) containing Et_3N (1.0 mL, 7.3 mmol) and methanesulfonyl chloride (0.42 mL, 5.4 mmol) was stirred at 0 °C for 1 h, whereupon saturated aqueous $NaHCO_3$ (15 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with 10% aqueous HCl (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried ($MgSO_4$) and

concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to afford 1.3 g (93%) of the mesylate as a pale yellow oil: ^{1}H NMR (300 MHz) δ 4.06 (dd, J = 4.4, 10.2 Hz, 1 H), 3.97 (dd, J = 6.5, 10.2 Hz, 1 H), 3.78−3.74 (m, 1 H), 3.64 (s, 3 H), 3.08 (s, 3 H), 2.92 (s, 3 H), 2.11−2.06 (br s, 1 H), 1.45−1.41 (m, 1 H), 1.02−0.96 (m, 1 H), 0.89−0.81 (m, 1 H), 0.80 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (75 MHz) δ 173.3, 72.5, 69.7, 61.5, 37.3, 32.5, 25.6, 23.5, 18.0, 13.7 10.6, −4.5, −4.8; IR (neat) ν 2955, 1740, 1660 cm^{-1}; mass spectrum (CI) m/z 382.1711 (base) ($C_{15}H_{32}NO_6SiS$ + H requires 382.1720).

[1*S*-(1α,2*β*,1′*β*)]-2-[2′-Azido-1′-(*tert*-butyldimethylsiloxy)]ethylcyclopropane-1-*N*-methoxy-*N*-methylcarboxamide (24). A mixture of the mesylate (1.3 g, 3.4 mmol) in DMF (25 mL) containing NaN_3 (2.2 g, 34 mmol) was heated to 65 °C for 12 h. The mixture was cooled to room temperature and Et_2O (150 mL) added. The mixture was filtered, and the resulting filtrate was washed with water (2 × 60 mL) and brine (2 × 60 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude residue was purified by flash chromatography using hexanes/EtOAc (6:1) as eluant to yield 0.89 g (81%) of **24** as a yellow oil: ^{1}H NMR (300 MHz) δ 3.66 (s, 3 H), 3.66−3.59 (m, 1 H), 3.26 (dd, J = 3.9, 12.4 Hz, 1 H), 3.15 (dd, J = 6.4, 12.4 Hz, 1 H), 3.12 (s, 3 H), 2.08−2.05 (br s, 1 H), 1.52−1.47 (m, 1 H), 1.09−1.04 (m, 1 H), 0.95−0.88 (m, 1 H), 0.83 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz) δ 173.4, 71.1, 61.5, 57.1, 32.4, 25.6, 24.8, 17.9, 13.9, 11.2, −4.7, −4.8; IR (neat) ν 2960, 2100, 1655, 1110, 830 cm^{-1}; mass spectrum (CI) m/z 329.2009 (base) ($C_{14}H_{28}N_3O_3Si$ + H requires 329.2009).

[1*S*-(1α,2*β*,1′*β*)]-2-[2′-Azido-1′-(*tert*-butyldimethylsiloxy)]ethylcyclopropyl-1-carboxylic Acid. Solid *tert*-BuOK (2.4 g, 22 mmol) was slowly added to stirred solution of **24** (0.89 g, 2.7 mmol) in THF (30 mL) containing H_2O (98 μL, 5.4 mmol) at 0 °C. After 30 min, 10% aqueous HCl was slowly added until pH 3, and the reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (2 × 60 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 0.69 g (90%) of the crude acid as a light yellow oil. The crude product was judged to be >95% pure by ^{1}H NMR and used without further purification: ^{1}H NMR (300 MHz) δ 9.85−9.55 (br s, 1 H), 3.62−3.58 (m, 1 H), 3.32 (dd, J = 4.4, 12.5 Hz, 1 H), 3.21 (dd, J = 5.9, 12.5 Hz, 1 H), 1.66−1.60 (m, 1 H), 1.57−1.52 (m, 1 H), 1.26−1.17 (m, 1 H), 1.10−1.03 (m, 1 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz) δ 179.9, 71.0, 57.0, 26.1, 25.6, 17.9, 16.8, 12.3, −4.6, −4.7; IR (neat) ν 3500−2800, 2100, 1695 cm^{-1}; mass spectrum (CI) m/z 286.1584 ($C_{12}H_{23}N_3O_3Si$ + H requires 286.1587), 240 (base).

[1*S*-(1α,2*β*,1′*β*)]-2-(2′-Azido)ethan-1′-ol-cyclopropane-1-carboxylic Acid (25). A solution of the acid from the previous experiment (0.69 g, 2.4 mmol) in CH_2Cl_2 (12 mL) containing an excess of HF-pyridine (1.0 mL) was stirred for 12 h. Water (6 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 0.33 g (81%) of **25** as a light yellow oil. The crude product was judged to be >95% pure by ^{1}H NMR and was used without further purification: ^{1}H NMR (300 MHz) δ 8.30−7.45 (br s, 1 H), 3.53−3.36 (comp, 3 H), 1.67−1.60 (comp, 2 H), 1.28−1.22 (m, 1 H), 1.15−1.11 (m, 1 H); ^{13}C NMR (75 MHz) δ 179.5, 70.9, 56.4, 25.4, 17.1, 12.3; IR (neat) ν 3700−2720, 2100, 1695, 1080, 1030 cm^{-1}; mass spectrum (CI) m/z 172.0730 ($C_6H_9N_3O_3$ + H requires 172.0722), 154 (base).

[1*S*-(1α,2*β*,1′*β*)]-2-[2′-*N*-(*tert*-Butoxycarbonyl)amino]-ethan-1′-ol-cyclopropane-1-carboxylic Acid (26). A suspension of Pd/C (5 mg) in dry EtOAc (1 mL) was degassed three times and stirred under H_2 (1 atm) for 1 h. A solution of **25** (90 mg, 0.53 mmol) and Boc_2O (0.14 g, 0.63 mmol) in EtOAc (1 mL) was added dropwise, and the resulting mixture was stirred vigorously under H_2 (1 atm) for 36 h. The solution was filtered through a pad of Celite, which was washed with EtOAc (7 mL). The filtrate was concentrated under reduced pressure to yield a thick yellow oil. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:3) to yield 0.11 g (87%) of **26** as a white solid: mp 118−120 °C; ^{1}H NMR (300 MHz) δ 5.04 (br s, 1 H), 3.47−3.36 (comp, 2 H), 3.21−3.14 (m, 1 H), 1.65−1.60 (m, 1 H), 1.58−1.53 (m, 1 H), 1.44 (s, 9 H) 1.25−1.20 (m, 1 H), 1.11−1.08 (m, 1 H); ^{13}C NMR (75 MHz) δ 179.1, 157.3, 80.2, 71.9, 46.4, 28.3, 25.8, 16.8, 12.3; IR (Nujol) ν 3458, 2982, 1698 cm^{-1}; mass spectrum (CI) m/z 246.1343 ($C_{11}H_{19}O_5N$ + H requires 246.1341), 172 (base).

***N*-[(1*S*-(1α,2*β*,1′*β*))-2-[2′-*N*-(*tert*-Butoxycarbonyl)amino]-ethan-1′-olcyclopropan-1-oyl]-L-phenylalanine-L-leucine Methyl Ester.** To solution of **26** (25 mg, 0.10 mmol) in dry DMF (1.5 mL) containing HOBt (44 mg, 0.33 mmol) and Phe-Leu-OMe (39 mg, 0.13 mmol) at −10 °C was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (27 mg, 0.13 mmol) in one portion. The mixture was allowed to warm to room temperature and stir for 12 h, whereupon the solution was partitioned between EtOAc (7 mL) and brine (3 mL). The aqueous layer was extracted EtOAc (2 × 7 mL), and the combined organic layers were washed with 10% citric acid (2 × 7 mL), saturated aqueous $NaHCO_3$ (2 × 7 mL), and brine (2 × 7 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (25:1) to yield 31 mg (60%) of the coupled product as a white solid: mp 85−88 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.29−7.19 (comp, 5 H), 6.45 (br s, 1 H), 4.67 (dd, J = 5.5, 9.1 Hz, 1 H), 4.47−4.43 (m, 1 H), 3.67 (s, 3 H), 3.19−3.11 (comp, 3 H), 2.90−2.82 (comp, 2 H), 1.65−1.53 (comp, 4 H), 1.44 (s, 9 H), 1.18−1.13 (m, 1 H), 0.98−0.94 (m, 1 H), 0.93 (d, J = 6.2 Hz, 3 H), 0.90 (d, J = 6.2 Hz, 3 H), 0.88−0.84 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 174.3, 173.7, 158.5, 138.4, 130.4, 129.3, 127.6, 80.1, 73.2, 55.7, 52.6, 52.1, 47.5, 41.4, 39.1, 28.8, 25.8, 25.5, 23.3, 21.9, 19.6, 11.5; IR ($CHCl_3$) ν 3424, 2960, 1740, 1682, 1510 cm^{-1}; mass spectrum (CI) m/z 520.3018 ($C_{27}H_{41}N_3O_7$ + H requires 520.3023).

***N*-[(1*S*-(1α,2*β*,1′*β*))-2-(2′-Amino)ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine Methyl Ester.** To a solution of the pseudopeptide from the preceding experiment (31 mg, 0.06 mmol) in CH_2Cl_2 (0.2 mL) at room temperature was added TFA (0.2 mL) and the mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the crude residue was triturated with Et_2O (3 × 2 mL) to yield light yellow solid. The residue was dissolved in EtOAc (2 mL) and was washed with saturated aqueous $NaHCO_3$ (2 × 1 mL) and brine (1 × 1 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford 24 mg (95%) of amino pseudopeptide as an off-white solid. This material was shown to be >95% pure by ^{1}H NMR and did not require further purification: mp 68−70 °C (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.18 (comp, 5 H), 4.70−4.65 (m, 1 H), 4.47−4.43 (m, 1 H), 3.68 (s, 3 H), 3.36−3.34 (m, 1 H), 3.16 (dd, J = 5.3, 13.5 Hz, 1 H), 2.99−2.78 (comp, 3 H), 1.68−1.55 (comp, 4 H), 1.22−1.16 (m, 1 H), 1.04−0.98 (m, 1 H), 0.92 (d, J = 6.3 Hz, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.91−0.88 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 174.4, 173.8, 138.5, 130.4, 129.4, 127.1, 74.9, 55.7, 52.7, 52.2, 48.0, 41.5, 39.0, 25.9, 25.6, 23.3, 21.8, 19.6, 11.6; IR (Nujol) ν 3305, 1735, 1676, 1638, 1560 cm^{-1}; mass spectrum (CI) m/z 420.2489 (($C_{22}H_{33}N_5O_5$ + H requires 420.2498).

[1*S*-(1α,2α,3*β*)]-2-Hydroxymethyl-3-phenylcyclopropane Hydrazide. To a solution of **28** (0.50 g, 2.9 mmol) in MeOH (10 mL) at room temperature was added hydrazine monohydrate (0.83 mL, 17 mmol) over 10 min. The mixture was stirred at room temperature for 12 h and was concentrated under reduced pressure to yield 0.56 g (ca. 95%) of the crude hydrazide as an off-white solid. This material was >95% pure by ^{1}H NMR and was used without further purification: mp 85−88 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.27−7.23 (comp, 3 H), 7.18−7.11 (comp, 2 H), 3.94 (dd, J = 6.1, 11.5 Hz, 1 H), 3.81 (dd, J = 7.5, 11.5 Hz, 1 H), 2.57 (t, J = 5.7 Hz, 1 H), 1.98 (dd, J = 5.3, 9.1 Hz, 1 H), 1.91−1.83 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.6, 141.5, 129.4, 127.3, 60.3, 32.7, 29.0, 28.8; IR (Nujol) ν 3288, 1675, 1625, 1540, 1100, 1034 cm^{-1}; mass spectrum (CI) m/z 207.1123 ($C_{11}H_{14}N_2O_2$ + H requires 207.1134).

[1*S*-(1α,6α,7*β*)]-2-Aza-3-oxo-7-phenyl-4-oxabicyclo[4.1.0]-heptane (29). To a suspension of the crude acyl hydrazide (0.30 g, 1.5 mmol) in H_2O/Et_2O (1:1, 8 mL total) at 0 °C was added $NaNO_2$ (0.15 g, 2.3 mmol) portionwise. A solution of 6 N HCl (2.3 mmol) was then added dropwise. Upon completion of the addition, the mixture was stirred for 30 min at 0 °C, and cold $CHCl_3$ (15 mL) was added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL). The organic layers were combined and washed with 5% aqueous $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to half volume, whereupon a volume of toluene (20 mL) was added. The remaining chloroform was removed under reduced pressure, and an additional portion of toluene (10 mL) was added. The reaction mixture was heated at 80 °C for 14 h, whereupon the reaction mixture was concentrated under reduced pressure, and the residual yellow solid was purified by flash chromatography eluting with hexanes/EtOAc (1:1.5) to yield 0.22 g (87%) of **29** as a white solid: mp 163−165 °C; ^{1}H NMR (300 MHz) δ 7.31−7.18 (comp, 3 H), 7.00 (d, J = 7.2 Hz, 2 H), 6.61 (br s, 1 H), 4.78 (dd, J = 6.1, 11.9 Hz, 1 H), 4.28 (dd, J = 4.5, 11.9 Hz, 1 H), 3.04 (dt, J = 2.7, 8.9 Hz, 1 H), 2.20 (dd, J = 3.2, 4.8 Hz, 1 H), 1.98−1.90 (m, 1 H); ^{13}C NMR (75 MHz) δ 154.7, 138.1, 128.5, 126.5, 125.6, 68.2, 36.2, 32.6, 18.1; IR ($CHCl_3$) ν 3431, 1716 cm^{-1}; mass spectrum (CI) m/z 190.0867 ($C_{11}H_{11}NO_2$ + H requires 190.0868), 129 (base).

[1*S*-(1α,2α,3*β*)]-1-Amino-2-hydroxymethyl-3-phenylcyclopropane (30). A solution of **29** (0.50 g, 0.030 mmol) in dioxane/H_2O (2:1, 18 mL total) containing $Ba(OH)_2 \cdot 8H_2O$ (1.7 g, 0.060 mmol) was heated at reflux for 4 h. The mixture was cooled to room temperature and filtered through a thin pad of Celite and washed with CH_2Cl_2 (20 mL). The layers of filtrate were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to yield 0.41 g (90%) of **30** as a light yellow oil. This material was shown to be >95% pure by ^{1}H NMR and did not require further purification: ^{1}H NMR (300 MHz) δ 7.29−7.14 (comp, 3 H), 7.03 (d, J = 7.4 Hz, 2 H), 4.20 (dd, J = 2.6, 11.6 Hz, 1 H), 4.02 (dd, J = 4.9, 11.6 Hz, 1 H), 2.84 (dd, J = 3.4, 7.2 Hz, 1 H), 2.23−2.17 (m, 1 H), 1.38−1.33 (m, 1 H); ^{13}C NMR (75 MHz) δ 141.4, 128.2, 125.8, 125.6, 59.9, 38.4, 29.4, 27.3; IR ($CHCl_3$) ν 3440, 3029, 1534 cm^{-1}; mass spectrum (CI) m/z 164.1075 ($C_{10}H_{13}$-NO + H requires 164.1075).

[1*S*-(1α,2α,3*β*)]-1-[*N*-(*tert*-Butoxycarbonyl)-L-leucine methyl ester]-2-hydroxymethyl-3-phenylcyclopropane (32) and [1*R*-(1α,2α,3*β*)]-1-[*N*-(*tert*-Butoxycarbonyl)-L-leucine methyl ester]-2-hydroxymethyl-3-phenylcyclopropane (36). To a solution of 5(*R*)-methyl oxopentanoate[26] (1.3 g, 9.2 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added Tf_2O (0.92 mL, 9.2 mmol) over the course of 5 min. The reaction mixture was stirred for 10 min, and 2,6-lutidine (1.1 mL, 9.2 mmol) was added dropwise. The mixture was stirred for an additional 10 min at 0 °C, whereupon *i*-Pr_2NEt (1.6 mL, 9.8 mmol) and **30** (1.0 g, 6.1 mmol) in CH_2Cl_2 (12 mL) were added. The mixture was allowed to warm to room temperature and was stirred 12 h. The mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed successively with water (1 × 15 mL), saturated aqueous $NaHCO_3$ (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield a bright yellow oil. The crude oil was purified by flash chromatography eluting with hexane/EtOAc (3:1) to yield 1.2 g (65%) of secondary amines as an inseparable mixture (5:1) of diastereomers as a clear oil. A solution of the diastereomeric amines (1.0 g, 3.4 mmol) and Boc_2O (2.3 g, 10 mmol) in CH_3CN (11 mL) was stirred at room temperature for 36 h. An additional portion of Boc_2O (2.3 g, 10 mmol) was added, and the mixture was stirred another 36 h. The solvent was removed under reduced pressure to yield a light yellow oil. The crude oil was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to yield 0.94 g (71%) of **32** and 0.19 g (14%) of **36**.

For **32:** pale yellow oil; ^{1}H NMR (300 MHz) δ 7.30−7.26 (m, 2 H), 7.21−7.18 (m, 1 H), 7.05−7.02 (m, 2 H), 4.21 (br s, 1 H), 4.03 (dd, J = 9.0, 11.0 Hz, 1 H), 3.81 (m, 1 H), 3.73 (s, 3 H), 3.57 (br s, 1 H), 3.04 (dd, J = 4.4, 7.0 Hz, 1 H), 1.94 (br s, 1 H), 1.87 (ddd, J = 5.6, 8.6, 14.3 Hz, 1 H), 1.80 (br s, 1 H), 1.75−1.70 (m, 1 H), 1.66−1.59 (m, 1 H), 1.47 (s, 9 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.9, 157.8, 139.4, 128.6, 126.3, 125.8, 82.1, 60.5, 60.4, 52.1, 44.8, 39.3, 33.4, 28.2, 26.2, 25.2, 23.0, 21.9; IR ($CHCl_3$) ν 3449, 2960, 1742, 1676, cm^{-1}; mass spectrum (CI) m/z 392.2445 ($C_{22}H_{33}NO_5$ + H requires 392.2437).

For **36**: yellow oil; ^{1}H NMR (300 MHz) δ 7.29−7.16 (comp, 3 H), 7.05−7.01 (comp, 2 H), 4.05 (dd, J = 3.0, 12.1 Hz, 1 H), 3.93 (dd, J = 5.4, 12.1 Hz, 1 H), 3.71 (s, 3 H), 3.52−3.47 (m, 1 H), 3.08 (dd, J = 4.1, 6.8 Hz, 1 H), 2.00−1.79 (comp, 4 H), 1.65−1.57 (m, 1 H), 1.44 (s, 9 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.69 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 171.7, 156.5, 139.2, 128.5, 126.3, 125.7, 82.1, 60.5, 60.1, 52.0, 46.0, 39.4, 35.0, 28.2, 27.0, 24.9, 23.2, 21.5; IR ($CHCl_3$) ν 3455, 3030, 2960, 1743, 1674 cm^{-1}; mass spectrum (CI) m/z 392.2437 ($C_{22}H_{33}N_1O_5$ + H requires 392.2437), 320, 292 (base).

[1*S*-(1α,2α,3*β*)]-1-[*N*-(*tert*-Butoxycarbonyl)-L-leucine methyl ester]-2-carboxy-3-phenylcyclopropane (33). To a solution of **32** (0.16 g, 0.41 mmol) in $CH_3CN/CHCl_3/H_2O$ (1:1:1.5; 12.5 mL total) at room temperature were added $NaHCO_3$ (0.22 g, 2.7 mmol), $NaIO_4$ (0.48 g, 2.3 mmol), and $RuCl_3$ (9.0 mg, 0.041 mmol). The mixture was stirred vigorously for 30 min, whereupon an additional 0.1 equiv of $RuCl_3$ (9.0 mg, 0.041 mmol) was added, and the mixture was stirred for 1 h. The mixture was diluted with EtOAc (5 mL) and the aqueous layer was adjusted to pH 4 with 10% aqueous HCl. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 7 mL). The organic layers were combined, washed with brine (2 × 7 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a light yellow oil. The crude oil was purified by flash chromatography eluting with hexane/EtOAc (1:1) to yield 0.14 g (85%) of **33** as a pale yellow oil: ^{1}H NMR (300 MHz) δ 7.33−7.26 (comp, 3 H), 7.09 (d, J = 6.8 Hz, 2 H), 4.40 (br s, 1 H), 3.76 (s, 3 H), 3.31 (br s, 1 H), 2.93 (app t, J = 5.5 Hz, 1 H), 2.40 (br s, 1 H), 1.89−1.76 (comp, 4 H), 1.45 (s, 9 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.87 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.3, 173.1, 155.6, 137.1, 128.8, 127.3, 126.3, 81.7, 59.9, 52.4, 45.1, 38.9, 33.0, 31.8, 28.0, 25.3, 22.8, 22.0; IR ($CHCl_3$) ν 3500−3300, 2958, 1736, 1702 cm^{-1}; mass spectrum (CI) m/z 404.2074 ($C_{22}H_{31}NO_6$−H requires 404.2073), 179 (base).

[1*S*-(1α,2α,3*β*)]-2-[(Allyloxycarbonyl)amino]-1-[*N*-(*tert*-Butoxycarbonyl)-L-leucine methyl ester]-3-phenylcyclopropane (34). To a solution of **33** (85 mg, 0.21 mmol) in acetone/H_2O (10:1; 0.5 mL total) at 0 °C were added Et_3N (35 μL, 0.25 mmol) and EtO_2CCl (26 mL, 0.27 mmol). The mixture was stirred for 1 h, whereupon NaN_3 (20 mg, 0.32 mmol) in H_2O (0.13 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C, and cold H_2O (1 mL) and CH_2Cl_2 (2 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL), and the organic layers were combined. The organic layers were dried ($MgSO_4$), anhydrous toluene (2 mL) was added, and the mixture was concentrated under reduced pressure. Allyl alcohol (0.5 mL) was added, and the mixture was heated at reflux 12 h. The mixture was cooled to room temperature and concentrated under reduced pressure to yield a light yellow oil. The crude oil was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to yield 82 mg (85%) of **34** as clear oil: ^{1}H NMR (300 MHz) δ 7.29−7.12 (comp, 5 H), 6.07 (br s, 1 H), 5.90 (ddd, J = 5.7, 10.5, 16.2 Hz, 1 H), 5.27 (d, J = 16.2 Hz, 1 H), 5.18 (d, J = 10.5 Hz, 1 H), 4.57 (d, J = 4.8 Hz, 2 H), 3.74 (s, 1 H), 3.45 (br s, 1 H), 2.96 (br s, 1 H), 2.21 (br s, 1 H), 1.90−1.70 (comp, 3 H), 1.65−1.55 (m, 1 H), 1.45 (s, 9 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.80 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.7, 156.5, 156.4, 138.0, 133.0, 128.7, 126.6, 126.5, 117.6, 81.4, 65.6, 52.4, 38.9, 38.3, 28.1, 25.3, 23.0, 21.4; IR ($CHCl_3$) ν 3685, 1717, 1693, 1537 cm^{-1}; mass spectrum (CI) m/z 461.2652 ($C_{25}H_{36}N_2O_6$ + H requires 461.2652), 361 (base).

***N*-[1*S*-(1α,2α,3*β*)]-2-[*N*-(*tert*-Butoxycarbonyl)-L-tyrosine-*t*-butyl ether-L-glycine-L-glycine]-3-phenylcyclopropane-1-*N*-(*tert*-Butoxycarbonyl)-L-leucine Methyl Ester (35).**

To a solution of Boc-Tyr(O-*t*-Bu)-Gly-Gly-OH (25 mg, 0.056 mmol) in CH_2Cl_2 (1 mL) at room temperature were added HOBt (8.0 mg, 0.056 mmol) and DCC (12 mg, 0.56 mmol). The mixture was stirred for 1 h at room temperature, whereupon it was transferred via syringe to a flask charged with **34** (20 mg, 0.043 mmol). $Pd(PPh_3)_4$ (10 mg, 8.7×10^{-3} mmol) and Bu_3SnH (13 μL, 0.047 mmol) were added, and the resulting mixture was stirred at room temperature for 6 h, filtered, and concentrated under reduced pressure to yield a bright yellow semisolid. The crude product was purified by flash chromatography eluting with CH_2Cl_2/MeOH (25:1) to afford 27 mg (78%) of **35** as a clear glass: ^{1}H NMR (500 MHz, CD_3OD) δ 7.29 (t, J = 7.2 Hz, 2 H), 7.23−7.14 (m, 1 H), 7.15−7.10 (comp, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 4.26 (dd, J = 5.4, 8.6 Hz, 1 H), 4.11−3.90 (comp, 4 H), 3.78 (s, 3 H), 3.79−3.71 (br s, 1 H), 3.11 (dd, J = 5.8, 13.9 Hz, 1 H), 2.96 (app t, J = 5.8 Hz, 1 H), 2.80 (dd, J = 9.2, 13.9 Hz, 1 H), 2.37 (br s, 1 H), 1.87−1.77 (comp, 2 H), 1.61−1.57 (m, 1 H), 1.45 (s, 9 H), 1.36−1.30 (m, 1 H), 1.34 (s, 9 H), 1.29 (s, 9 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.76 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.0, 174.8, 171.8, 158.0, 157.8, 155.3, 139.3, 133.7, 130.9, 129.7, 127.8, 127.3, 125.2, 82.7, 80.8, 79.5, 57.8, 53.6, 43.7, 43.6, 39.2, 38.7, 38.3, 34.7, 31.0, 29.2, 28.7, 28.6, 26.5, 23.3; IR ($CHCl_3$) ν 3428, 3013, 2930, 1735, 1690 cm^{-1}; mass spectrum (CI) m/z 810.4653 ($C_{43}H_{64}N_5O_{10}$ requires 810.4653).

General Procedure for Deprotecting Pseudopentapeptides to 7, 8, 10−14. To a solution of the pseudopentapeptide (1 equiv) in CH_2Cl_2 (0.1 M) at room temperature was added TFA (10 equiv), and the mixture was stirred at room temperature for 30 min to 2 h. The solvent was removed under reduced pressure, and the crude residue was triturated with Et_2O (3 × 1 volume) to yield a light yellow solid that was dissolved in EtOAc (2 volumes). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 1 volume) and brine (2 × 1 volume). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the resulting product was recrystallized from MeOH/Et_2O.

***N*-[(1*S*-(1α,2α,1′α))-2-[2′-(L-Tyrosine)amino]ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester (7)** was prepared in 92% yield from the protected pseudopeptide as an off-white solid: mp 120−122 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.32−7.18 (comp, 5 H), 7.09 (d, J = 8.5 Hz, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 4.64−4.59 (m, 1 H), 4.49−4.46 (m, 1 H), 4.11 (app t, J = 7.1 Hz, 1 H), 3.66 (s, 3 H) 3.55−3.53 (m, 1 H), 3.38−3.34 (m, 1 H), 3.20−3.12 (comp, 3 H), 2.97−2.85 (comp, 2 H), 1.74−1.55 (comp, 4 H), 1.05−1.00 (comp, 2 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.93−0.89 (m, 1 H), 0.89 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.6, 174.3, 173.9, 173.8, 157.4, 131.4, 130.4, 129.5, 129.4, 127.8, 116.3, 69.5, 57.8, 55.9, 52.7, 52.2, 45.9, 41.6, 41.2, 38.9, 25.9, 24.9, 23.2, 21.9, 20.3, 11.0; IR (Nujol) ν 2998, 1730, 1690 cm^{-1}; mass spectrum (CI) m/z 583.3119 ($C_{31}H_{42}N_4O_7$ + H) requires 583.3132), 294 (base).

***N*-[1*S*-(1α,2α,3*β*)]-2-(L-Tyrosine-L-glycine-L-glycine)-3-phenylcyclopropane-1-L-leucine methyl ester (8)** was prepared in 90% yield from the protected pseudopeptide as a white solid: mp 101−103 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.30−7.14 (comp, 5 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.76 (d, J = 8.4 Hz, 2 H), 4.07−4.00 (comp, 3 H), 3.92−3.83 (comp, 3 H), 3.72 (s, 3 H), 3.14 (dd, J = 6.4, 14.6 Hz, 1 H), 3.11 (dd, J = 4.6, 6.6 Hz, 1 H), 2.96 (dd, J = 8.0, 14.6 Hz, 1 H), 2.82 (dd, J = 4.6, 6.1 Hz, 1 H), 1.77−1.70 (comp, 2 H), 1.66−1.61 (comp, 2 H), 0.95 (d, J = 6.3 Hz, 3 H), 0.93 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.0, 175.0, 172.8, 170.0, 155.7, 139.3, 133.7, 130.9, 129.7, 127.8, 127.3, 125.2, 57.8, 53.6, 46.7, 43.6, 39.2, 38.7, 38.3, 34.7, 31.0, 26.5, 23.3 ; IR (Nujol) ν 3028, 2950, 1730, 1665 cm^{-1}; mass spectrum (CI) m/z 554.2987 ($C_{29}H_{39}N_5O_6$ + H requires 554.2979).

***N*-[(1*R*-(1α,2α,1′α))-2-[2′-(L-Tyrosine)amino]ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester (10)** was prepared in 90% yield from the protected pseudopeptide as an off-white solid: mp 106−108 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.37−7.20 (comp, 5 H), 7.09 (d, J = 8.6 Hz, 2 H), 6.76 (d, J = 8.6 Hz, 2 H), 4.63 (dd, J = 5.7, 8.8 Hz, 1 H), 4.46 (dd, J = 5.7, 9.5 Hz, 1 H), 4.07 (dd, J = 6.6, 8.0 Hz, 1 H), 3.66 (s, 3 H) 3.56−3.53 (m, 1 H), 3.38−3.34 (m, 1 H), 3.27−3.15 (comp, 3 H), 3.14−2.85 (comp, 2 H), 1.74−1.57 (comp, 5 H), 1.05−1.00 (m, 2 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.5, 174.0, 169.9, 158.3, 138.4, 131.6, 130.3, 129.6, 127.8, 126.1, 116.8, 69.2, 56.2, 56.0, 52.7, 52.3, 46.2, 41.6, 39.0, 38.0, 25.8, 24.9, 23.3, 22.0, 20.5, 10.4; IR (Nujol) ν 2998, 1730, 1690 cm^{-1}; mass spectrum (CI) m/z 583.3119 ($C_{31}H_{42}N_4O_7$ + H requires 583.3132), 294 (base).

***N*-[(1*S*-(1α,2*β*,1′*β*))-2-[2′-(L-Tyrosine)amino]ethan-1′-ol-cyclopropan-1-oyl]-L-phenylalanine-L-leucine methyl ester (11)** was prepared in 93% yield from the protected pseudopeptide as an off-white solid: mp 118−121 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.28−7.16 (comp, 5 H), 7.09 (d, J = 8.6 Hz, 2 H), 6.77 (d, J = 8.6 Hz, 2 H), 4.71−4.66 (m, 1 H), 4.47−4.42 (m, 1 H), 3.99 (t, J = 6.8 Hz, 1 H), 3.69 (s, 3 H), 3.40 (dd, J = 4.0, 13.6 Hz, 1 H), 3.21−3.09 (comp, 3 H), 3.00−2.81 (comp, 3 H), 1.68−1.55 (comp, 4 H), 1.20−1.13 (m, 1 H), 1.02−0.96 (m, 1 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 3 H), 0.88−0.82 (m, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.0, 174.5, 173.8, 169.9, 158.3, 138.5, 131.6, 130.4, 129.4, 127.7, 126.0, 116.9, 72.7, 56.0, 52.7, 52.2, 46.5, 41.3, 39.0, 37.9, 25.9, 25.7, 23.3, 21.8, 19.8, 11.5; IR (Nujol) ν 3420, 2960, 1730, 1678 cm^{-1}; mass spectrum (CI) m/z 583.3118 ($C_{31}H_{42}N_4O_7$ + H requires 583.3132), 212 (base).

***N*-[5-(L-Tyrosine)amino-(4*S*)-hydroxy]pentan-1-oyl-L-phenylalanine-L-leucine methyl ester (12)** was prepared in 89% yield from the protected pseudopeptide as a crystalline solid: mp 81−83 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.33−7.17 (comp, 5 H), 7.02 (d, J = 8.4 Hz, 2 H), 6.70 (d, J = 8.4 Hz, 2 H), 4.66 (dd, J = 5.6, 9.2 Hz, 1 H), 4.44 (dd, J = 6.0, 8.2 Hz, 1 H), 3.67 (s, 3 H), 3.50 (dd, J = 6.8, 13.5 Hz, 1 H), 3.47−3.44 (m, 1 H), 3.18−3.03 (comp, 2 H), 2.93−2.81 (comp, 2 H), 2.71 (dd, J = 7.4 Hz, 13.5 Hz, 1 H), 2.31−2.17 (comp, 2 H), 1.69−1.44 (comp, 5 H), 0.93 (d, J = 6.2 Hz, 3 H), 0.89 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.7, 174.4, 173.8, 157.4, 138.5, 131.4, 130.3, 129.4, 129.2, 127.7, 116.4, 70.6, 57.8, 55.7, 52.7, 52.2, 46.0, 41.5, 38.9, 32.9, 31.3, 25.9, 23.3, 21.9; IR (Nujol) ν 1647, 1550 cm^{-1}; mass spectrum (CI) m/z 571.3133 ($C_{30}H_{42}N_4O_7$ + H requires 571.3132), 293 (base).

***N*-[5-(L-Tyrosine)amino-(4*R*)-hydroxy]pentan-1-oyl-L-phenylalanine-L-leucine methyl ester (13)** was prepared in 90% yield from the protected pseudopeptide as a chalky solid: mp 79−81 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.26−7.17 (comp, 5 H), 7.02 (d, J = 8.2 Hz, 2 H), 6.71 (d, J = 8.2 Hz, 2 H), 4.65 (dd, J = 5.4, 9.2 Hz, 1 H), 4.45 (dd, J = 6.1, 7.9 Hz, 1 H), 3.67 (s, 3 H), 3.55−3.44 (comp, 2 H), 3.18−3.07 (comp, 2 H), 2.93−2.72 (comp, 3 H), 2.23 (t, J = 7.5 Hz, 2 H), 1.69−1.44 (comp, 5 H), 0.93 (d, J = 6.1 Hz, 3 H), 0.89 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.3, 175.6, 174.4, 173.9, 157.4, 138.5, 131.4, 130.3, 129.4, 129.1, 127.7, 116.4, 70.5, 57.7, 52.7, 52.2, 45.9, 41.5, 41.0, 38.9, 32.8, 31.3, 25.9, 23.3, 21.9; IR (Nujol) ν 1736, 1643, 1536 cm^{-1}; mass spectrum (CI) m/z 571.3133 ($C_{30}H_{42}N_4O_7$ + H requires 571.3132), 293 (base).

***N*-[5-(L-Tyrosine)amino-(4*R*)-hydroxy-(3*R*)-methyl]pentan-1-oyl-L-phenylalanine-L-leucine methyl ester (14)** was prepared in 92% yield from the protected pseudopeptide as a light yellow solid: mp 68−70 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.37 (d, J = 8.0 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 1 H), 7.37−7.15 (comp, 5 H), 7.09 (d, J = 8.4 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 4.67 (dd, J = 5.4, 9.1 Hz, 1 H), 4.52−4.41 (m, 1 H), 3.99−3.94 (m, 1 H), 3.67 (s, 3 H), 3.48−3.42 (m, 1 H), 3.16 (dd, J = 5.7, 14.1 Hz, 1 H), 3.11−3.01 (comp, 3 H), 2.90 (dd, J = 8.2, 13.4 Hz, 1 H), 2.87 (dd, J = 9.6, 14.1 Hz, 1 H), 2.47 (q, J = 7.1 Hz, 1 H), 1.69−1.55 (comp, 4 H), 1.51−1.45 (m, 1 H), 1.37−1.33 (comp, 2 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 179.2, 174.3, 173.8, 170.0, 158.3, 138.5, 131.5, 130.4, 129.4, 127.7, 126.1, 116.9, 68.7, 56.1, 55.5, 52.7, 52.2, 49.6, 46.4, 41.5, 39.2, 38.7, 38.1, 38.0, 25.9, 23.2, 21.8, 17.7; IR (Nujol) ν 3540, 2940, 1731, 1695 cm^{-1}; mass spectrum (CI) m/z 585.3276 ($C_{31}H_{44}N_4O_7$ + H requires 585.3288).

[(1*S*-(1α,2α,1′α))-2-[2′-Azido-1′-(*tert*-Butyldimethylsiloxy)]-ethyl-cyclopropane-1-carboxylic Acid Methyl Ester (37).

A solution of **17** (0.25 g, 1.6 mmol) in MeOH (10 mL) containing concentrated HCl (5 drops) was stirred for 12 h at room temperature. After cooling to 0 °C, saturated aqueous $NaHCO_3$ was added until pH 8 and the mixture was concentrated under reduced pressure to remove the volatiles. The resulting aqueous layer mixture was then extracted with EtOAc (3 × 7 mL), and the organic layers were combined. The organic layer was then washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield 0.24 g of a yellow oil. To a solution of the crude oil (0.24 g, 1.3 mmol) in DMF (3 mL) were added imidazole (0.18 g, 2.6 mmol) and TBDMSCl (0.26 g, 1.7 mmol), and the solution was stirred for 12 h at room temperature. Et_2O (10 mL) was added, and the organic layer was washed with H_2O (2 × 4 mL) and brine (2 × 4 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with hexanes/EtOAc (10:1) to afford 0.33 g (70% over two steps) of **37** as a light yellow oil: ^{1}H NMR (300 MHz) δ 3.92−3.86 (m, 1 H), 3.68 (s, 3 H), 3.22 (dd, J = 4.1, 12.5 Hz, 1 H), 3.05 (dd, J = 5.2, 12.5 Hz, 1 H), 1.81 (dt, J = 5.9, 8.0 Hz, 1 H), 1.46 (p, J = 6.4 Hz, 1 H), 1.21−1.12 (comp, 2 H), 0.91 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz) δ 173.2, 70.8, 57.3, 51.9, 25.8, 24.8, 18.1, 18.0, 13.6, −4.2, −4.7; IR ($CHCl_3$) ν 2954, 2104, 1722 cm^{-1}; mass spectrum (CI) m/z 300.1742 ($C_{13}H_{25}N_3O_3Si$ + H requires 300.1743), 168 (base).

***N*-[(1*S*-(1α,2α,1′α))-2-[(2′-[*N*-(*tert*-Butoxycarbonyl)-L-tyrosine]amino)-1′-(*tert*-butyldimethylsiloxy)]ethyl-cyclopropane-1-carboxylic Acid Methyl Ester.** To a solution of **37** (0.12 g, 0.40 mmol) in MeOH (2 mL) was added 10% Pd/C (10 mg (cat.)) and the mixture was stirred under H_2 (1 atm). The reaction mixture was stirred vigorously for 1 h and was then filtered through a Celite pad. The Celite pad was washed with MeOH (2 mL), and the filtrate was concentrated under reduced pressure to yield a light yellow oil. The oil was dissolved in DMF (2 mL) and was cannulated into a solution of Boc-Tyr(O-*t*-Bu)-OH (0.18 g, 0.52 mmol) and HOBt (0.17 g, 1.3 mmol) in DMF (2 mL) at 0 °C. EDCI (0.11 g, 0.52 mmol) was added in one portion, and the mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (5 mL) and brine (2 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL), and the organic layers were combined. The organic layer was washed with 10% citric acid (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), and brine (2 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with hexane/EtOAc (4:1) to yield 0.18 g (78%) of ester as a light yellow oil: ^{1}H NMR (300 MHz) δ 7.07 (d, J = 8.4 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.19 (br s, 1 H), 4.99 (d, J = 8.6 Hz, 1 H), 4.60−4.50 (m, 1 H), 4.28 (m, 1 H), 3.78 (p, J = 5.8 Hz, 1 H), 3.71 (s, 3 H), 3.35−3.27 (comp, 2 H), 3.13−2.82 (comp, 5 H), 1.75 (q, J = 6.2 Hz, 1 H), 1.37 (s, 9 H), 1.31 (s, 9 H), 1.28−1.12 (m, 1 H), 1.13−1.07 (comp, 2 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz) δ 173.1, 171.1, 155.3, 154.4, 131.5, 129.7, 124.0, 80.0, 78.2, 69.9, 56.1, 52.0, 45.2, 37.9, 28.9, 28.3, 25.8, 24.6, 18.3, 18.0, 13.5, −4.0, −4.7; IR ($CHCl_3$) ν 3433, 2930, 1720, 1674, 1505 cm^{-1}; mass spectrum (CI) m/z 593.3616 ($C_{31}H_{52}N_2O_7Si$ + H requires 593.3622), 537 (base).

***N*-[1*S*-(1α,2α,1′α)]-2-[(2′-[*N*-(*tert*-Butoxycarbonyl)-L-tyrosine]amino)-1′-(*tert*-butyldimethylsiloxy)]ethyl-cyclopropane-1-carboxylic Acid (38).** To a solution of methyl ester (0.15 g, 0.26 mmol) in EtOH (1.7 mL) at 0 °C was added dropwise a 1 M solution of NaOH (0.34 mL). The mixture was stirred at 0 °C for 2 h and then at room temperature for an additional 12 h. The mixture was concentrated under reduced pressure, and the resulting semisolid was dissolved in H_2O (1 mL); EtOAc (2 mL) was added. The pH of the aqueous layer was carefully adjusted to ca. 4 with 5% aqueous $KHSO_4$, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 2 mL), and the organic layers were combined. The organic layer was washed with brine (2 × 3 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield 0.14 g (90%) of **38** as a clear glass. This material was shown to be >95% pure by ^{1}H NMR and did not require further purification: mp 124−126 °C; ^{1}H NMR (300 MHz) δ 7.06 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 5.82−5.77 (m, 1 H), 5.24 (d, J = 9.5 Hz, 1 H), 4.30−4.22 (m, 1 H), 3.65−3.58 (m, 1 H), 3.54−3.45 (m, 1 H), 2.94 (d, J = 7.4 Hz, 2 H), 2.90−2.85 (m, 1 H), 1.76 (dt, J = 5.9, 7.8 Hz, 1 H), 1.40 (s, 9 H), 1.33 (s, 9 H), 1.29−1.20 (m, 1 H), 1.14−1.00 (comp, 2 H), 0.88 (s, 9 H), 0.09 (s, 9 H); ^{13}C NMR (75 MHz) δ 174.2, 171.3, 156.7, 154.4, 131.4, 129.7, 124.5, 81.1, 78.5, 69.8, 55.9, 46.2, 38.6, 28.9, 28.3, 25.8, 18.1, 17.9, 12.2, −4.3, −4.7; IR ($CHCl_3$) ν 3433, 2930, 1717, 1673, 1506 cm^{-1}; mass spectrum (CI) m/z 579.3465 ($C_{30}H_{50}N_2O_7Si$ + H requires 579.3466).

Bis-Cyclopropane Adduct (39). To a solution of **38** (50 mg, 0.085 mmol) in CH_2Cl_2 (0.5 mL) at room temperature were added HOBt (11 mg, 0.085 mmol) and DCC (18 mg, 0.085 mmol). The mixture was stirred for 1 h at room temperature, whereupon it was transferred via syringe to a flask charged with **34** (30 mg, 0.065 mmol) in CH_2Cl_2 (0.5 mL). $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) and Bu_3SnH (19 μL, 0.072 mmol) were added, and the resulting mixture was stirred at room temperature for 3 h. The mixture was filtered and concentrated under reduced pressure to yield a bright yellow semisolid. The crude product was purified by flash chromatography eluting with hexane/EtOAc (4:1) to afford 46 mg (75%) of **39** as a clear glass: mp 112−114 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.29 (app t, J = 7.4 Hz, 3 H), 7.21−7.18 (comp, 2 H), 7.10 (d, J = 8.2 Hz, 2 H), 6.86 (d, J = 8.2 Hz, 1 H), 4.50 (br s, 1 H), 4.24 (dd, J = 5.0, 9.4 Hz, 1 H), 3.93 (ddd, J = 3.4, 5.4, 8.9 Hz, 1 H), 3.77 (s, 3 H), 3.71 (br s, 1 H), 3.37 (dt, J = 6.4, 13.5 Hz, 1 H), 3.16−3.02 (comp, 2 H), 2.95 (br s, 1 H), 2.73 (dd, J = 9.6, 13.4 Hz, 1 H), 2.44 (br s, 1 H), 1.90−1.82 (comp, 2 H), 1.70−1.63 (comp, 3 H), 1.43 (s, 9 H), 1.32 (s, 9 H), 1.31−1.25 (m, 1 H), 1.28 (s, 9 H), 1.20−1.14 (m, 1 H), 1.06−1.03 (m, 1 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.91 (s, 9 H), 0.81 (d, J = 6.4 Hz, 3 H), 0.12 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.0, 157.5, 155.2, 139.6, 134.0, 130.9, 129.6, 127.7, 127.5, 125.1, 82.5, 80.6, 79.4, 71.4, 57.6, 53.3, 46.5, 39.1, 38.7, 31.6, 29.2, 28.7, 28.5, 26.6, 26.5, 25.3, 23.3, 21.8, 21.3, 18.9, 13.0, −3.7, −4.4; IR ($CHCl_3$) ν 3349, 2930, 1735, 1680, 1674, 1505 cm^{-1}; mass spectrum (FAB) m/z 973.5714 ($C_{51}H_{80}N_4O_{10}S$ + H requires 937.5722).

Enkephalin Analogue (9). To a solution of **39** (20 mg, 0.021 mmol) and NaI (19 mg, 0.13 mmol) in dry CH_3CN (0.25 mL) at room temperature was added freshly distilled TMSCl (0.14 mL, 0.10 mmol). The mixture was stirred for 1 h, whereupon the mixture was quenched with MeOH (1 mL) and concentrated under reduced pressure. The crude residue was diluted with EtOAc (1 mL) and washed with saturated sodium thiosulfate (2 × 0.5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield 10 mg (85%) of **9** as a white solid: mp 110−112 °C; ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.96 (d, J = 4.2 Hz, 1 H), 7.74 (app t, J = 5.4 Hz, 1 H), 7.22−7.20 (comp, 2 H), 7.14−7.11 (m, 1 H), 7.08−7.04 (comp, 2 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.64 (d, J = 8.4 Hz, 2 H), 3.58 (s, 3 H), 3.56−3.49 (m, 1 H), 3.33−3.30 (m, 1 H), 3.19−3.14 (m, 1 H), 2.98−2.92 (comp, 2 H), 2.85 (dd, J = 4.2, 13.5 Hz, 1 H), 2.44 (dd, J = 5.1, 13.5 Hz, 1 H), 2.42 (m, 1 H), 1.88 (app t, J = 4.8 Hz, 1 H), 1.74−1.64 (comp, 3 H), 1.47−1.43 (m, 1 H), 1.22 (br s, 1 H), 1.13−1.07 (m, 1 H), 0.99−0.95 (m, 1 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.84−0.81 (m, 1 H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 175.4, 173.8, 171.9, 155.7, 140.4, 130.1, 128.5, 128.1, 126.1, 125.5, 114.9, 67.3, 59.1, 56.1, 51.4, 44.5, 42.4, 41.0, 37.6, 31.0, 28.7, 24.3, 23.8, 22.6, 22.1, 19.0, 9.8; IR ($CHCl_3$) ν 3015, 1725, 1675 cm^{-1}; mass spectrum m/z (CI) 567.3202 ($C_{31}H_{42}N_4O_6$ + H requires 567.3183) (base).

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Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR and IR spectra and mass spectral data) for new compounds not included in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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