Cyclopropane-Derived Peptidomimetics. Design, Synthesis, and Evaluation of Novel Ras Farnesyltransferase Inhibitors

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Trisubstituted cyclopropanes have previously been established as rigid replacements of dipeptide arrays in several biological systems. Toward further evaluating the utility of these dipeptide mimics in the design of novel CA_1A_2X-based inhibitors of Ras farnesyltransferase (FTase), the conformationally constrained, diastereomeric pseudopeptides CAbuΨ[COcpCO]FM **7**−**9**, the flexible analogue CAbuΨ[$CHOHCH_2$]FM (**10**), and the tetrapeptide CAbuFM (**6**) were prepared. The orientations of the two peptide backbone substituents and the phenyl group on the cyclopropane rings in **7**−**9** were specifically designed to probe selected topological features of the hydrophobic binding pocket of the A_2 subsite of FTase. The syntheses of the requisite trisubstituted cyclopropane carboxylic acid **22** and the diastereomeric cyclopropyl lactones **32a**,**b** featured diastereoselective intramolecular cyclopropanations of chiral allylic diazoacetates and a new method for introducing side chains onto the *C*-terminal amino acid of cyclopropane-derived dipeptide replacements via the opening of an *N*-Boc-aziridine with an organocuprate. These cyclopropane intermediates were then converted into the targeted FTase inhibitors **7**−**9** by standard peptide coupling techniques. The pseudopeptides **7**−**9** were found to be competitive inhibitors of Ras FTase with IC_{50}s of 1055 nM for **7**, 760 nM for **8**, and 7200 nM for **9**. The flexible analogue **10** of these constrained inhibitors exhibited a IC_{50} of 320 nM and hence was slightly more potent than **7** and **8**. All of these pseudopeptides were less potent than the tetrapeptide parent CAbuFM (**6**), which had an IC_{50} of 38 nM. Because **7** and **8** are approximately equipotent, it appears that the orientation of the peptide backbone substituents on the cyclopropane rings in **7** and **8** do not have any significant effect on binding affinity and that multiple binding modes are possible without significant changes in affinity. On the other hand, this flexibility does not extend to the orientation of the side chain of the A_2 residue as **7** and **8** were both nearly 1 order of magnitude more potent than **9**. Comparison of the relative potencies of **6** and **10** suggests that the amide linkage between the A_1 and the A_2 residues of CA_1A_2X-derived FTase inhibitors is important.

Introduction

The development of conformationally constrained mimics of peptide secondary structure is central to the process of mutating small, biologically active peptides into nonpeptidic substances that have comparable or enhanced binding affinity for the same enzyme active site or macromolecular receptor.[1] Most such replacements have been designed to imitate or initiate turns or helices, but several have been reported that stabilize extended structures.[2] A survey of the vast majority of peptide mimics reveals that most are dedicated to controlling backbone organization, and few are capable of orienting the amino acid side chains, which contribute critical recognition elements for binding and specificity. Thus, there is a general need for peptide replacements that predictably constrain both the peptide backbone and the side chains in orientations that correspond to the biologically active conformation, or the bound structure, of the peptide.

Toward this end, we invented a novel class of cyclopropane-derived peptide isosteres related to **2**.[3,4] These dipeptide mimics differ from the traditional peptide bond replacements in that the cyclopropane ring in **2** replaces the nitrogen and α-carbon atoms in the peptide backbone of the dipeptide **1** as well as the *β*-carbon of the amino acid (Yaa). Hence, we have modified the usual abbreviation for designating simple peptide bond replacements and use the formulation −Xaa*ψ*[COcpCO]Yaa− to indicate the presence of a cyclopropane ring as a subunit in these dipeptide mimics. When the cyclopropane substituents corresponding to the peptide chain on **2** are trans, the backbone *ϕ* angle is locked to enforce a local *β*-strand conformation, an important secondary structural element

(1) For some recent reviews of peptide mimics, see: (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720. (c) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169−2187. (d) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *38*, 12789−12854. (e) Goodman, M.; Zhang, J. *Chemtracts—Org. Chem.* **1997**, *10*, 629−645.

(2) For example, see: (a) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568−6570. (b) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947−9962. (c) Chen, L.; Trilles, R. V. *Tetrahedron Lett.* **1995**, *36*, 8715−8718. (d) Boumendjel, A.; Roberts, J. C.; Hu, E.; Pallai, P. V.; Rebek, J., Jr. *J. Org. Chem.* **1996**, *61*, 4434−4438. (e) Janetka, J. W.; Raman, P.; Satyshur, K.; Flentke, G. R.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 441−442.

(3) Martin, S. F.; Austin, R. E.; Oalmann, C. J. *Tetrahedron Lett.* **1990**, *31*, 4731−4734.

(4) Martin, S. F.; Hom, R. K. *Tetrahedron Lett.* **1999**, *40*, 2887−2890.

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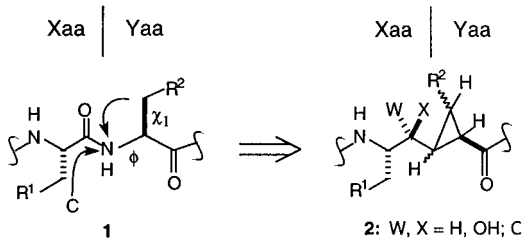
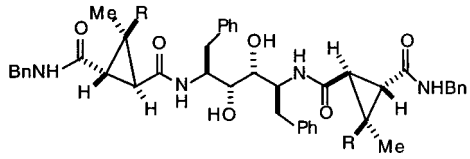
found in proteins and numerous inhibitors bound at enzyme active sites.[5] In the corresponding cis-isomer, a reverse turn may be initiated. Depending on the stereochemistry at the cyclopropyl carbon bearing R^2 in **2**, this side chain may be positioned *relative to the backbone* in orientations that approximate χ_1 angles in **1** of gauche(−) (−60°) or gauche(+) (+60°). Of these two orientations, the gauche(−) conformation is more commonly encountered in oligo and polypeptides than the sterically more congested gauche(+) conformation.[6]



1 **2:** W, X = H, OH; C

To establish the efficacy of dipeptide replacements related to **2**, we developed methods for their enantioselective synthesis and then introduced them into a number of biologically active pseudopeptides, including inhibitors of renin, HIV-1 protease, and matrix metalloproteinases as well as enkephalin analogues.[7−10] Others have used such cyclopropane-derived mimics in non-peptide fibrinogen receptor antagonists.[11] The predicted structural properties of these rigid replacements were verified in a significant study in which truncated analogues of **2** were incorporated in conformationally restricted inhibitors of HIV-1 protease. For example, the two pseudopeptides **3** and **4**, which contain *two* cyclopropane replacements, were subnanomolar inhibitors.[8] The structure of **3** in solution was determined by NMR, and the structure of the complex of **4** bound to HIV-1 protease was established by X-ray crystallography. Except at two terminal benzyl groups, the solution conformation of **3** was nearly identical to the enzyme-bound structures of **4** and other closely related flexible HIV-1 protease inhibitors. Thus, the two cyclopropane rings in **3** and **4** stabilize an extended, β-strand conformation in solution that corresponds with high fidelity to their biologically active conformation.

Having established that isosteric replacements related to **2** mimicked secondary structural elements found in



3: R = Me
4: R = H

the enzyme-bound structures of selected pseudopeptides, we were intrigued by the possibility that these replacements might be used as tools to probe the topology of the bound conformation of peptide-derived inhibitors of other biologically important proteins. In this context, we became interested in Ras farnesyltransferase (FTase), a 21 kD G-protein that catalyzes the farnesylation of a cysteine residue at the *C*-terminus of Ras proteins, the critical step in the posttranslational modification of Ras that leads to translocation of Ras to the membrane. If Ras farnesylation is blocked, oncogenic Ras proteins do not acquire their transforming ability, so the development of potent inhibitors of FTase has emerged as an important strategy for discovery of potential anticancer agents.[12] Many inhibitors of FTase are based upon the *C*-terminal tetrapeptide Cys-Val-Ile-Leu, CVIL, of the H-Ras p21 substrate, and such compounds are commonly referred to as CA_1A_2X mimetics. The middle two amino acids A_1A_2 are typically hydrophobic residues with X usually being Met. Numerous derivatives of the tetrapeptide Cys-Val-Phe-Met, CVFM (**5**), have been found to be potent inhibitors of FTase, several of which cause complete tumor regression in vivo.[12]

Central to the design of novel ligands as FTase inhibitors is knowledge of their bound conformation, and there are various studies that suggest such inhibitors may bind to the active site in extended *and* turn-like conformations.[13,14] Perhaps most informative are the detailed insights emanating from recent X-ray crystal-

(5) For a review, see: Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472.

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(13) For example, see: (a) Nigam, M.; Seong, C.-M.; Qian, Y.; Hamilton, A. D.; Sebti, S. M. *J. Biol. Chem.* **1994**, *268*, 20695−20698. (b) Qian, Y.; Blaskovich, M. A.; Saleem, M.; Seong, C. M.; Wathen, S. P.; Hamilton, A. D.; Sebti, S. M. *J. Biol. Chem.* **1994**, *269*, 12410−12413. (c) Qian, Y.; Vogt, A.; Sebti, S.; Hamilton, A. *J. Med. Chem.* **1996**, *39*, 217−223. (d) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Bock, R. L.; Conner, M. W.; Davide, J. P.; Hamilton, K.; Koblan, K. S.; Kohl, N. E.; Kral, A. M.; Mosser, S. D.; Omer, C. A.; Pompliano, D. L.; Rands, E.; Schaber, M. D.; Shah, D.; Wilson, F. R.; Gibbs, J. B.; Graham, S. L.; Hartman, G. D.; Oliff, A. I.; Smit, R. L. *J. Med. Chem.* **1996**, *39*, 1345−1348. (e) Burns, C.; Guitton, J.; Baudoin, B.; Lelievre, Y.; Duchesne, M.; Parker, F.; Fromage, N.; Commercon, A. *J. Med. Chem.* **1997**, *40*, 1763−1767. (f) Dinsmore, C.; Williams, T.; Hamilton, K.; O'Neill, T.; Rands, E.; Koblan, K.; Kohl, N.; Gibbs, J.; Graham, S.; Hartman, G.; Oliff, A. *Bioorg. Med. Chem. Lett.* **1997**, *10*, 11345-1348. (g) Byk, G.; Lelievre, Y.; Duchesne, M.; Clerc, F.; Scherman, D.; Guitton, J. D. *Bioorg. Med. Chem.* **1997**, *5*, 115−124.

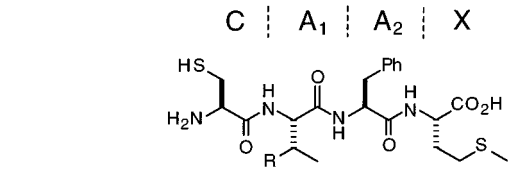
(14) For example, see: (a) Stradley, S. J.; Rizo, J.; Gierasch, L. M. *Biochemistry* **1993**, *32*, 12586−12590. (b) James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, G. W.; Lucas, B. K.; Levinson, A. D.; Marsters, J. C. *Science* **1993**, *260*, 1937−1942. (c) Marsters, J. C., Jr.; McDowell, R. S.; Reynolds, M. E.; Oare, D. A.; Somers, T. C.; Stanley, M. S.; Rawson, T. E.; Struble, M. E.; Burdick, D. J.; Chan, K. S.; Duarte, C. M.; Paris, K. J.; Tom, J. Y. K.; Wan, D. T.; Xue, Y.; Burnier, J. P. *Bioorg. Med. Chem.* **1994**, *2*, 949−957. (d) Koblan, K. S.; Culberson, J. C. Desolms, S. J.; Giuliani, E. A.; Mosser, S. D.; Omer, C. A.; Pitzenberger, S. M.; Bogusky, M. J. *Protein Science* **1995**, *4*, 681−688. (e) Liu, R.; Dong, D. L.-Y.; Sherlock, R.; Nestler, H. P.; Genarri, C.; Mieglo, A.; Scolastico, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 847−852. (f) O'Connell, C. E.; Ackermann, K.; Rowell, C. A.; Garcia, A. M.; Lewis, M. D.; Schwartz, C. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2095−2100.

lographic studies that were not available at the time the present work was initiated. In the ternary complex of *N*-acetyl-Cys-Val-Ile-selenoMet-COOH, α-hydroxyfarnesylphosphonic acid, and FTase, the tetrapeptide was found to bind in an extended conformation.[15] Because of the conformational changes that occur on complexation of this CVIM analogue, the authors noted that there may be alternate inhibitor binding modes for inhibitors related to CVFM, which have an aromatic residue rather than isoleucine at the A_2 position. More recent structural work with complexes of other CVIM and farnesyl pyrophosphate analogues with rat FTase reveals that the peptides can bind in either an extended or a *β*-turn conformation depending upon whether the enzyme contains the active site zinc ion that coordinates with the SH group of the *C*-terminal cysteine.[16]

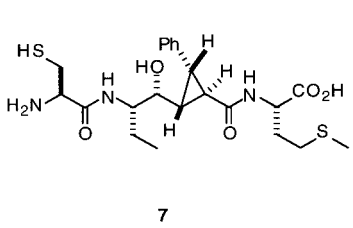
Inhibitor Design and Synthesis

Identification of Target CVFM (5) Analogues. Although it was not evident at the outset of our studies whether peptide-derived FTase inhibitors bound preferentially in extended or turn-like conformations, it was known that the orientation of the phenyl group on the Phe residue played an important role in determining the potency of CVFM derivatives.[17] Hence, to probe selected topographical requirements about the Phe subunit of such inhibitors, we decided to examine conformationally constrained CVFM analogues containing extended and turn-like replacements **2** (R^2 = Ph) at the A_1 and A_2 subsites. Based upon synthetic considerations, we selected the tetrapeptide sequence **6**, CAbuFM, as the template for designing cyclopropane-containing analogues of CVFM (**5**). The replacement of valine in the CVFM parent **5** with α-aminobutyric acid, Abu, in **6** was not anticipated to be deleterious because previous work had shown that a number of hydrophobic residues may be introduced at the A_1 position of CVFM derivatives without significant changes in binding affinity.[18,19]

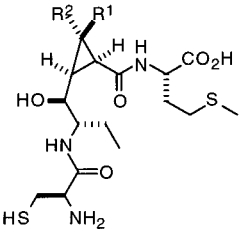
Incorporation of an −AbuΨ[COcpCO]Phe− as the dipeptide replacement **2** at the A_1 and A_2 subsites of **6** led to a number of potential pseudopeptide analogues of **6**. However, we selected compounds **7**−**9** as the initial targets of our inquiry because they would be readily accessible and they seemed most likely to mimic the biologically active conformation of **6**. The cyclopropane ring in **7** was predicted to stabilize a local extended conformation while orienting the phenyl group in approximately a gauche(−) orientation. In **8** and **9**, the cis relationship of the backbone substituents was anticipated to induce a turn in the chain. As in **7**, the orientation of the phenyl group in **8** is gauche(−). The pseudopeptide **9** was selected to assess the consequence upon binding affinity of placing the phenyl group in a gauche(+) orientation. The route to **7** was not readily amenable to the syntheses of epimers of **7** in which the stereochemistry of the cyclopropylcarbinol was the same as in **8** and **9** or in which the configuration at the carbon bearing the phenyl group was inverted. It was necessary to prepare the pseudopeptide **10** as a flexible control to provide a better measure of the specific effects of introducing the rigid −AbuΨ[COcpCO]Phe− replacement because the A_1−A_2 amide bond of **6** in the CVFM analogues **7**−**9** is replaced with a constrained hydroxyethylene moiety. In each of the pseudopeptides **7**−**10**, the carbonyl group of the A_2 residue, which forms a hydrogen bond to Arg202*β* of rat FTase and is important for biological activity,[15,16,18] is retained.



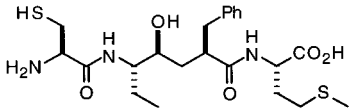
5: R = Me
6: R = H



7



8: R^1 = H, R^2 = Ph
9: R^1 = Ph, R^2 = H



10

Syntheses of Cyclopropane-Derived Pseudopeptides 7−9. The first task to be addressed in the synthesis of the pseudopeptide **7** was the preparation of the syn allylic diazoester **16**. Following literature precedent,[20] we found addition of lithium phenylacetylide added to **11** in THF containing hexamethylphosphorus triamide (HMPT) proceeded without racemization to give a mixture (9:1) of **12** (74% yield) together with lesser amounts of the anti isomer **13** (8%) (Scheme 1). HMPT was employed to enhance "nonchelation"-controlled addition,[21] although we found 18-crown-6 could be used in place of HMPT to give similar product ratios.[20a] To establish the relative stereochemistry of **12** and **13**, they were converted into their respective acetonides ((i) Amberlyst/H^+, MeOH; (ii) 2,2-dimethoxypropane, pyridinium *p*-toluenesulfonate) **14**

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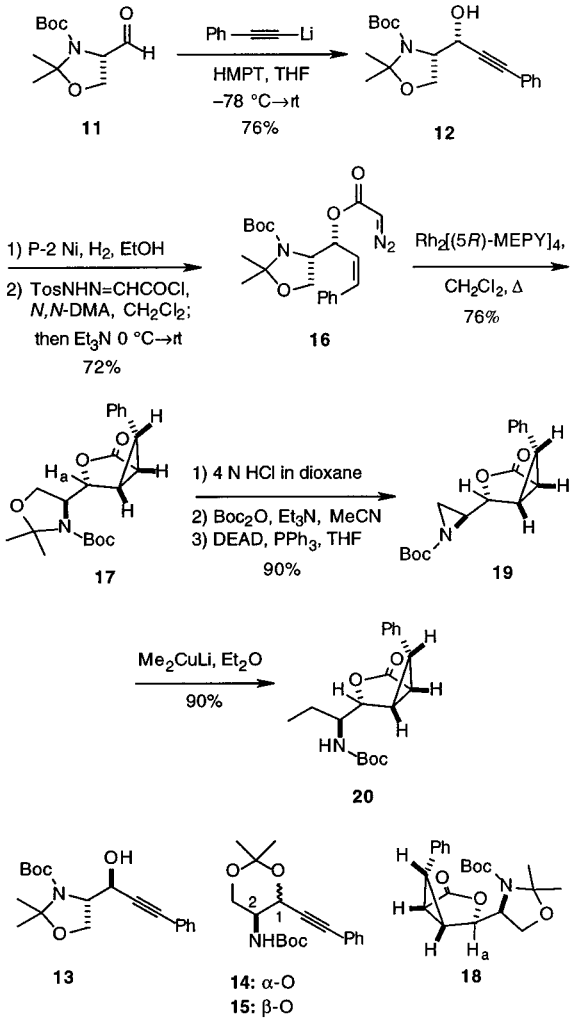
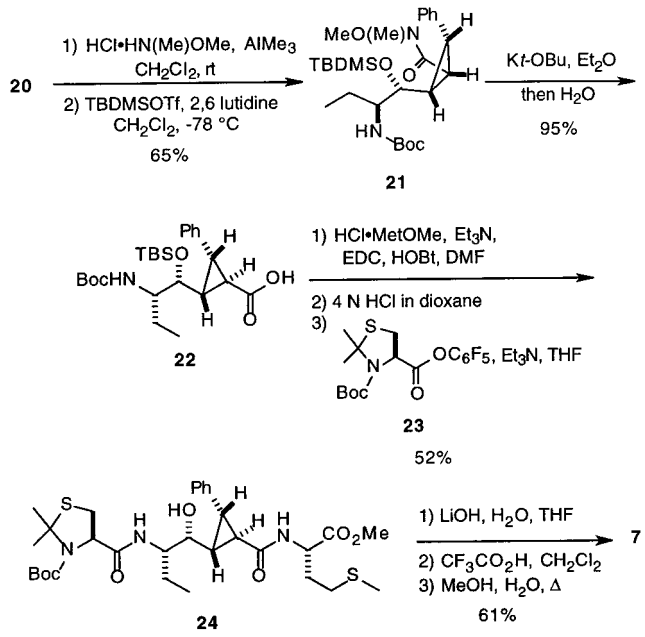
Scheme 1



Scheme 2



and **15**, and the vicinal coupling constants for the protons at the two stereogenic centers were determined (**14**, $J_{1,2}$ = 9.3 Hz; **15**, $J_{1,2}$ = 2.9 Hz).[20a] The syn adduct **12** was then reduced stereoselectively using P-2 Ni[22] to provide an intermediate *Z*-allylic alcohol that was converted into the diazoester **16** (72% overall) by the procedure of Corey and Myers.[23] When **16** was heated in the presence of Rh_2[(5*R*)-MEPY]$_4$,[24] a mixture (8:1) of diastereomeric cyclopropyl lactones **17** and **18**, which were readily separable, was obtained in 76% combined yield. Stereochemical assignments were based on the established trends that have been observed in the relative chemical shifts of the proton H_a in the two isomers: H_a in an exo isomer consistently appears upfield from H_a in the corresponding endo isomer [e.g., $\delta(H_a)$ in **17** = 4.26 ppm, **18** = 4.71 ppm].[25] If the cyclization of **16** was conducted in the presence of the enantiomeric Rh_2[(5*S*)-MEPY]$_4$ catalyst, a mixture (3:1) of **17** and **18** was obtained in only 25% yield, thus reflecting a "mis-matched" catalyst–substrate interaction similar to that observed in previous work.[25] Cyclization of **16** in the presence of the achiral catalyst $Cu(TBS)_2$ also gave a mixture (3:1) of **17** and **18**, but in 84% combined yield. Thus, there is a clear preference for the formation of the exo diastereomer **17** in the catalyzed, intramolecular cyclopropanations of **16**. Elaboration of the Abu side chain in **20** was then accomplished by first converting the protected amino alcohol side chain of **17** into the aziridine **19** via a three-step sequence featuring a Mitsunobu cyclization;[26] it was not possible to cleave the *N*,*O*-acetal without concomitant cleavage of the *N*-Boc group. Subsequent ring opening of the intermediate aziridine with Gilman's reagent (Me_2CuLi) then furnished the cyclopropyl dipeptide **20** in 81% overall yield from **17**.[27]

Aluminum-mediated amidation of the lactone **20** according to the Weinreb protocol,[28] followed by protection of the intermediate secondary alcohol provided **21** in 66% overall yield (Scheme 2). Upon treatment with base under modified Gassman conditions,[29] **21** underwent thermodynamically driven epimerization at the cyclopropane carbon bearing the amide function, and subsequent hydrolysis of the amide proceeded spontaneously in situ to afford the acid **22** in 95% yield. The peptide backbone of **22** was now locally locked in the requisite extended motif. The *C*-terminal end of the dipeptide replacement **22** was coupled with the methyl ester of L-methionine, whereupon the *N*-terminus of the resultant tripeptide was deprotected and coupled with the pentafluorophenol ester of *N*-Boc-2,2-dimethylthiazolidine **23**[30] to give **24**

(22) Marvell, E. N.; Li, T. *Synthesis* **1973**, 457–468.
(23) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *23*, 3559–3562.
(24) For a general procedure for the synthesis of both Rh_2[(5*R*)-MEPY]$_4$ and Rh_2[(5*S*)-MEPY]$_4$, see: Doyle, M. P.; Winchester, W. R.; Protopopova, M. N. In *Organic Synthesis*; Boeckman, R. K., Ed.; John Wiley & Sons: New York, 1995; Vol. 73, pp 13–24.
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(26) (a) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513–6516. (b) Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544–2546.
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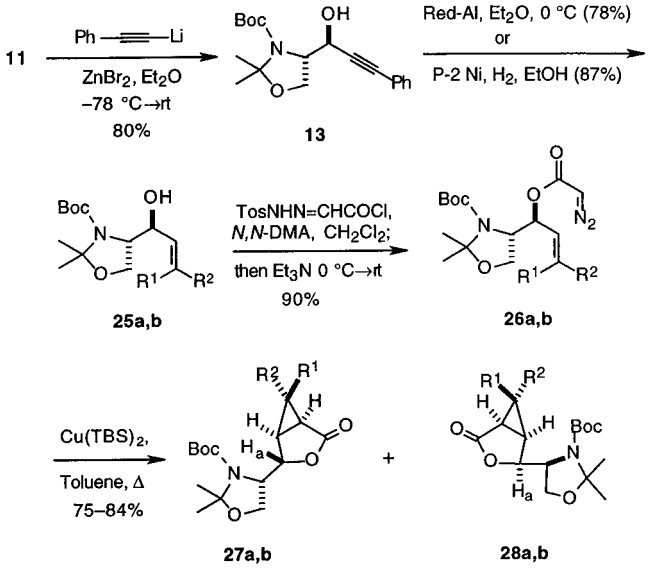
Scheme 3

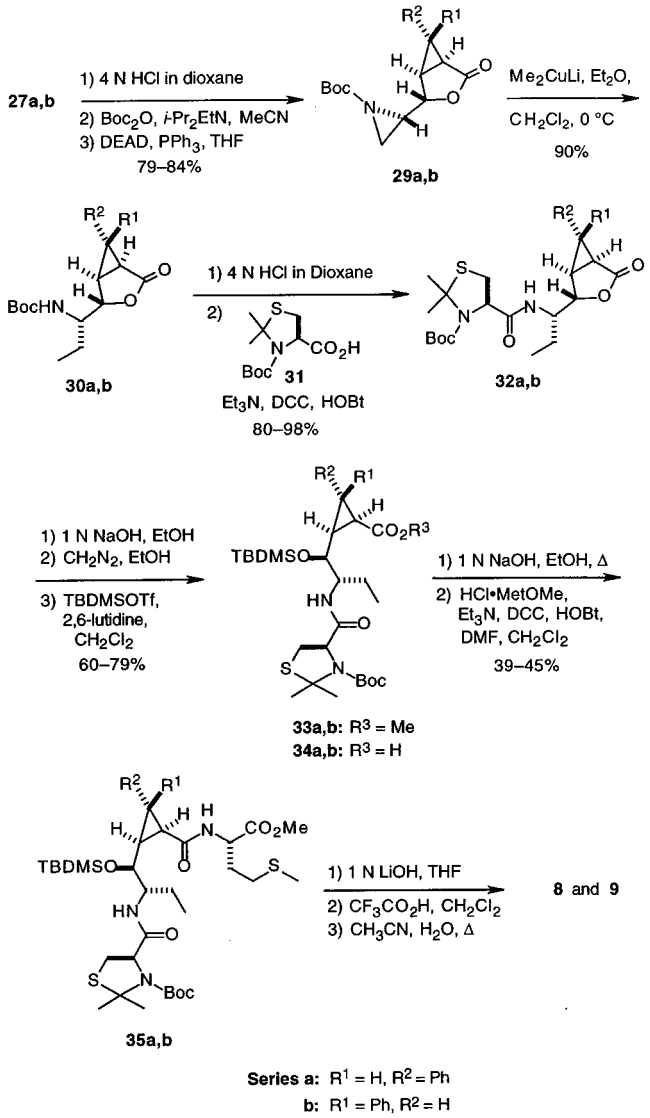


in 52% overall yield. Global deprotection of **24** delivered the desired CVFM analogue **7** as its trifluoroacetate salt in 61% yield after purification via reversed-phase HPLC.

Having thus prepared the extended CVFM analogue **7**, we focused on the synthesis of the turn-like derivatives **8** and **9**. Toward this end, it was necessary to employ the two diastereoisomeric allylic diazoacetates **26a**,**b**, which would be derived from the anti alcohol **13**, as substrates for the key intramolecular cyclopropanations. In the event, when the addition of lithium phenylacetylide to the aldehyde **11** was performed in the presence of $ZnBr_2$,[31] the reaction proceeded via a preferential chelation-controlled mode to give the anti product **13** (80% yield) together with lesser quantities of the syn product **12** (13%).[20a] Reduction of **13** with Red-Al gave **25a** in 78% yield,[32] whereas hydrogenation of **13** using P-2 Ni[22] provided the *cis*-alkene **25b** in 87% yield (Scheme 3). The allylic alcohols **25a**,**b** were then converted to their corresponding diazoacetates **26a**,**b** as before in about 90% yield.[23] When **26a** was heated in the presence of the achiral catalyst $Cu(TBS)_2$, a mixture (6:1) of **27a** and **28a** was obtained in 84% combined yield. Similarly, when **26b** was heated in the presence of $Cu(TBS)_2$, a mixture (8:1) of **27b** and **28b** was obtained. The structural assignments of the cyclized products were based on the observed chemical shifts of the diagnostic proton H_a (vide supra), which typically appears upfield in the ^1H NMR spectra of the exo diastereomers: $\delta(H_a)$ in **27a** = 4.61 ppm, **27b** = 4.66 ppm; **28a** = 4.24 ppm, **28b** = 4.62 ppm.[25b,c] Interestingly, use of the chiral catalysts Rh_2[(5*S* or 5*R*)-MEPY]$_4$ did not greatly enhance the diastereomeric ratios of the cyclopropyl lactone products.

The remaining steps in the conversion of **27a**,**b** into the pseudopeptide **8** and **9** are similar to the reactions developed for the synthesis of **7**. Thus, the Abu side chains in **30a**,**b** were elaborated from the protected amino alcohol side chains in **27a,b** by ring opening of the

Scheme 4



intermediate aziridines **29a**,**b** (Scheme 4). The correctness of previous stereochemical assignments were confirmed in part by an X-ray structure of the aziridine **29a**. Deprotection of the *N*-terminus of **30a**,**b** followed by coupling the intermediate amines with the cysteine derivative **31**[33] afforded the cyclopropyl lactone tripeptides **32a**,**b** in 98% and 80% yield, respectively. Hydrolysis of the lactone moieties of **32a**,**b** followed by esterification and protection of the secondary alcohol, which was necessary to prevent relactonization, gave **33a**,**b** (60% and 79%). Whereas the saponification of **33a** to give **34a** (64% yield) proceeded readily with 1 N NaOH in EtOH at room temperature, hydrolysis of **33b** required refluxing with base in EtOH overnight to furnish **34b** (47% yield). Not only was the hydrolysis of **33b** sluggish, perhaps due to the steric influence of the phenyl group proximal to the methyl ester, but it was also accompanied by a significant amount of epimerization.[34] The addition of more base or use of extended heating times led only to decreased yield and increased epimerization. Nevertheless, the final coupling of **34a**,**b** with the methyl ester

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(32) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595−4597.
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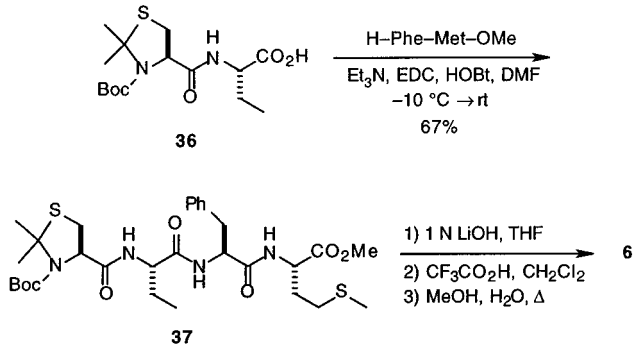
(34) The epimerized product could be separated from the desired carboxylic acid **34b** by silica gel chromatography.

Scheme 5



of L-methionine delivered **35a**,**b** in 71% and 84% yield, respectively. The deprotection and purification of the protected pseudopeptides **35a**,**b** was conducted as before to provide the desired turn-like CVFM analogues **8** and **9**. However, it was necessary to use acetonitrile rather than MeOH in the final stage of deprotecting the *N*,*S*-acetal and during the purification procedure in order to facilitate the azeotropic removal of water at lower temperatures; the hydroxy acids **8** and **9** underwent relatively facile lactonization on heating.

Synthesis of Reference Tetrapeptide Derivatives. The parent tetrapeptide CAbuFM (**6**) was prepared in a straightforward fashion using standard peptide coupling procedures. Thus, the dipeptide **36**, which was prepared by condensing **23** with the methyl ester of L-ethylglycine, and phenylalanyl methionine methyl ester, H-Phe-Met-OMe, were joined by EDC/HOBt-mediated coupling to give **36** in 67% yield (Scheme 5). Global deprotection of **37** followed by purification gave **6** as its trifluoroacetate salt in 17% overall yield.

The synthesis of the hydroxyethylene derivative **10** commenced with the alkylation of (*S*)-pseudophedrine-3-hydrocinnamide (**38**) with 1-bromo-2-pentene according to the Myers protocol to provide **39** (93% yield) as predominantly one diastereomer (14:1) according to chiral HPLC analysis of the crude product mixture (Scheme 6).[35] Bromolactonization of **39** afforded the α-bromo lactone **40** together with several inseparable minor isomers in 79% combined yield.[36] Displacement of the secondary bromide in **40** by NaN_3 followed by reduction of the azide gave an intermediate amine that was coupled with **23** to deliver **41** as a single isomer in 57% overall yield. Hydrolysis of the lactone ring in **41** gave a hydroxy butyric acid derivative that was transformed into the protected acid **42** by sequential treatment with TBDMSCl/imidazole/DMF and then glacial acetic acid/THF.[37] Coupling of **42** with the methyl ester of L-methionine gave the protected tetrapseudopeptide **43** in 82% yield. Deprotection of **43** to give **10** was achieved in a fashion similar to that described for the preparation of **8** and **9**.

Biological Activities of 6−10. The tetrapeptide **6** and the derived pseudopeptides **7**−**10** were evaluated as inhibitors of FTase in an in vitro assay that was conducted at Rhône-Poulenc Rorer. The assay employed was based upon a previously described protocol that had been modified to incorporate scintillation proximity assay (SPA) techniques using streptavidin-coated SPA beads.[38] The IC_{50} determinations are derived by measurement of inhibition of farnesylation from 8-point serial dilution of test compounds, and the results of these assays are summarized in Table 1. The tetrapeptide template **6** that

Scheme 6

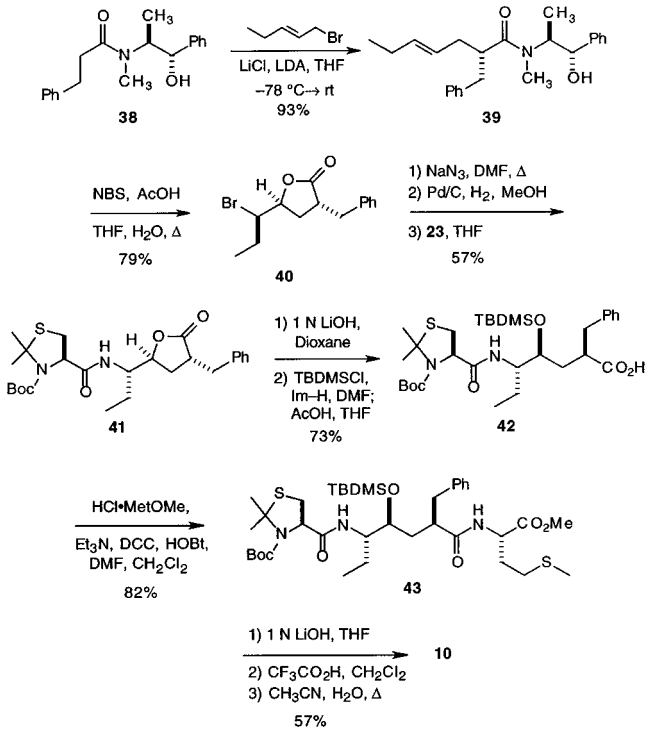


Table 1. Biological Activities of 6−10 as Inhibitors of FTase

inhibitor	IC_{50}[a] (nM)
6	38
10	320
7	1055
8	760
9	7200

[a] The IC_{50} values were determined from a single assay by measurement of inhibition of farnesylation from eight-point serial dilution of **6**−**10**.

was used as the basis for these studies is the most active being approximately equipotent with CVFM itself.[17] Compound **10**, which is the flexible equivalent of the constrained pseudopeptides **7**−**9**, was about 8-fold less potent than **6**. Hence, the mere replacement of the A_1−A_2 amide bond in **6** with a hydroxyethylene moiety as in **10** does not appear to be well tolerated. In the two cyclopropane-derived pseudopeptides **7** and **8,** the phenyl ring is oriented trans to the *C*-terminus, and these compounds were only 2−3-fold less active than **10**. However, compound **9**, in which the phenyl ring is cis to the *C*-terminus, is about 22 times less potent than **10**.

The relatively small difference in biological activity between the extended mimic **7** and the putative turn-like mimic **8** raises two questions: (1) Do the cyclopropane rings in these derivatives maintain the extended and turn-like conformations as they were intended? (2) Why are **7** and **8** essentially equipotent? To gain some preliminary structural insights to address the first question, **44**, which has the same stereochemistry at each of the stereogenic centers as those in the turn-like analogue **8**, was prepared via a Weinreb amidation[28] of **30a**. The X-ray structure of **44** (Figure 1b) reveals that the hydrogen of the secondary hydroxyl group is not within hydrogen bonding distance of the cis-amide carbonyl group on the adjacent carbon of the cyclopropane ring. Presumably the lack of this hydrogen bonding interaction

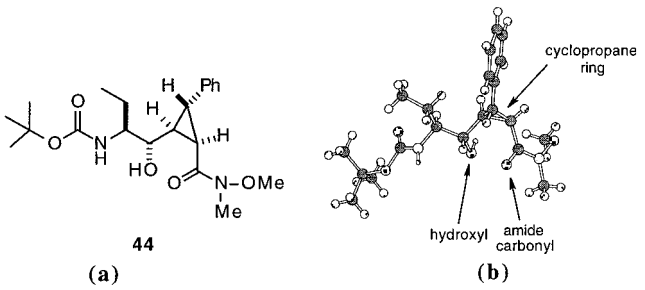
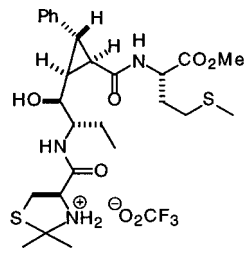


Figure 1. (a) Line drawing of **44**. (b) Chem 3D representation of the X-ray structure of **44** showing orientation of backbone and amide and hydroxyl functional groups.

coupled with unfavorable steric interactions between the *N*-terminal and *C*-terminal side chains conspire to provide a three-dimensional structure in which the backbone substituents are directed away from each another in an extended conformation rather than the desired turn-like array. The turn in the backbone chain is thus localized only about the cyclopropane ring itself, and the remainder of the molecule is free to adopt a number of conformations with an extended one being favored, at least in the solid state. However, this extended array might result from intermolecular packing forces that override any intramolecular interactions, so it is not possible to extrapolate this structure to the preferred conformation of **44** in solution.

To examine whether the cis-substituted cyclopropane found in compounds related to **44** and **8** might stabilize a turn-like structure in solution, an NMR study of **45**, which was prepared by reaction of **35a** with neat CF_3CO_2H, was conducted in DMSO-d_6. No NOE interactions between the protected cysteine and methionine residues that flank the cyclopropane ring in **45** could be detected; only intraresidue contacts were observed. Hence, while in DMSO-d_6 there does not appear to be a significant concentration of a turn-like structure in solution, this study does not exclude the possibility that a more turn-like structure of **45** might exist in an aqueous medium.



45

Inasmuch as the available structural data for compounds related to **8** do not support a turn-like conformation, **7** and **8** have comparable biological activity presumably because they can adopt similar, three-dimensional structures at the active site of FTase. The X-ray structure of the ternary complex of FTase with a CVIM derivative and α-hydroxyfarnesylphosphonic acid offers an opportunity to evaluate this hypothesis.[15] In this structure, there is an approximate 12 Å separation between the Cys thiol group, which associates with the zinc ion, and the *C*-terminal methionine carboxyl function that forms a salt bridge with Gln167α of the enzyme. Preliminary modeling of **7** and **8**, and hence **9**, revealed a number of extended conformers for each that can bridge this 12 Å distance. Three-dimensional structures for **7**−**9** were then generated using the extracted structure of the bound CVIM analogue as a template for the peptide backbones of **7**−**9**. These structures were then locally minimized and modeled back into the active site so that the Cys thiol group and the *C*-terminal carboxyl group of **7**−**9** make the necessary contacts with the enzyme. Although the phenyl ring in both **7** and **8** may be oriented so that it occupies part of the isoleucine binding pocket of FTase, it is not possible to place the phenyl ring of **9** in this hydrophobic pocket while positioning the backbone in the active site cleft. Thus, while the relative orientation of the backbone substituents on the cyclopropane rings of **7**−**9** does not appear to have a significant effect on binding affinity, the position of the phenyl ring relative to the backbone is critical. This observation is consistent with the report of Leftheris who examined a series of Phe constrained FTase inhibitors and found that changes in the orientation of the phenyl group in CA_1A_2X-based pseudopeptides had dramatic effects upon their relative potencies.[17]

Conclusions

Compounds **6**−**10** were prepared as novel CA_1A_2X-based inhibitors of Ras farnesyltransferase to probe the topological features of the hydrophobic binding pocket of the A_2 subsite. During the course of these synthetic studies, a novel method was developed for elaborating the *C*-terminal residue of cyclopropane-derived dipeptide replacements via the regioselective opening of aziridines with organocuprates. The cyclopropane-derived pseudopeptides **7**−**9** were designed as conformationally constrained derivatives of the tetrapeptide CAbuFM (**6**) by substituting the cyclopropane replacement −AbuΨ[COcpCO]Phe− for Abu-Phe. Compound **10**, which is the flexible analogue of **7**−**9**, served as the pseudopeptide benchmark for **6**, although direct comparison of the relative potencies of **6** and **10** suggests that replacing the A_1−A_2 amide linkage with a *S*-hydroxyethylene moiety is not well tolerated. In the FTase inhibitor **7**, the backbone substituents are trans, whereas these substituents in **8** and **9** are cis. The orientation of the phenyl group relative to the *C*-terminus of the pseudopeptide in **7** and **8** is positioned in an orientation that mimics a gauche(−) χ_1-angle very different from the gauche(+) orientation approximated in **9**.

The constrained pseudopeptides **7** and **8** are nearly equipotent inhibitors of FTase suggesting that the relative orientations of the peptide backbone substituents on the cyclopropane rings in **7** and **8** does not have a significant effect on binding affinity, presumably because of some flexibility in the FTase peptide binding pocket. However, changes in the orientation of the phenyl ring are not tolerated as evidenced by the fact that **7** and **8** were both nearly 1 order of magnitude more potent than **9**. The comparable biological activities of **7** and **8** coupled with the structural studies of **44** and **45** suggest that the

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(37) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615−4625.
(38) Roskoski, R., Jr.; Ritchie, P.; Gahn, L. G. *Anal. Biochem.* **1994**, *222*, 275−280.

cis-relationship of the backbone substituents on the cyclopropane rings of these compounds does not appear to enforce turn-like conformations. Whether other cis-substituted dipeptide replacements related to **2** might stabilize such conformations must be ascertained by further experimentation. Indeed, other applications of cyclopropane-derived dipeptide isosteres are under investigation, and these results will be reported in due course.

Experimental Section

General Methods. 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 internal standard Me_4Si (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: 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).[39] Percent yields are given for compounds that were ≥95% pure as judged by NMR.

***tert*-Butyl-(4*S*,1′*R*)- and -(4*S*,1′*S*)-2,2-dimethyl-4-(1′-hydroxy-3′-phenyl-2′-propynyl)oxazolidine-3-carboxylate (12 and 13).** To a solution of phenylacetylene (3.8 mL, 34.6 mmol) in THF (160 mL) at −78 °C was added with stirring 1.4 M *n*-BuLi in hexanes (28 mL, 38.2 mmol). After 1 h, 18-crown-6 (12.6 g, 47.6 mmol) was added in one portion, and the resulting brown slurry was stirred for 10 min. The aldehyde **11** (5.45 g, 23.8 mmol) in THF (10 mL) was added slowly over 15 min, whereupon the slurry became dark red in color. This mixture was stirred at −78 °C for 2 h, and a saturated solution of NH_4Cl (100 mL) was added. The cooling bath was removed, and the slurry was stirred until it reached rt. Water (25 mL) was added, and the mixture was extracted with ether (2 × 100 mL). The combined organics were washed with 1 N HCl (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with a gradient of 15% EtOAc/hexanes then 30% EtOAc/hexanes to give 6.0 g (76%) of **12** and 0.7 g (8%) of **13**.

For **12**: ^1H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.41−7.34 (comp, 5 H), 5.47 (d, J = 6.4 Hz, 1 H), 4.73 (dd, J = 3.4, 6.4 Hz, 1 H), 4.13−3.99 (comp, 2 H), 3.01 (s, 1 H), 1.52 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 151.4, 130.8, 128.0, 127.9, 122.1, 93.4, 89.6, 83.9, 78.9, 63.6, 61.1, 60.9, 27.6, 25.8; IR (neat) ν 3437, 2979, 1686, 1392, 1366, 1173, 1068 cm^{-1}; mass spectrum (CI) *m*/*z* 332.1862 ($C_{19}H_{25}NO_4$ + H requires 332.1862), 276, 258 (base), 232, 218, 156.

For **13**: ^1H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.40−7.34 (comp, 5 H), 5.55 (br s, 1 H), 4.92 (d, J = 4.4 Hz, 1 H), 4.17 (dd, J = 3.0, 9.0 Hz, 1 H), 4.02 (dd, J = 6.7, 9.0 Hz, 1 H), 3.97−3.94 (m, 1 H), 1.54 (s, 3 H), 1.44−1.42 (comp, 12 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 151.4, 130.7, 128.1, 127.9, 122.2, 93.5, 89.3, 83.9, 79.1, 63.6, 61.2, 60.5, 27.7, 25.8; IR (neat) ν 3427, 2977, 1686, 1393, 1366, 1171, 1056 cm^{-1}; mass spectrum (CI) *m*/*z* 332.1857 ($C_{19}H_{25}NO_4$ + H requires 332.1862), 276, 258 (base), 232, 218, 200, 156.

***cis*-[4*S*,4(1′*R*)]-4-(1′-Hydroxy-3′-phenyl-2′-propenyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester.** To a green suspension of $Ni(OAc)_2 \cdot 4H_2O$ (1.25 g, 5.03 mmol) in anhydrous EtOH (25 mL) was added 1 M $NaBH_4$ in 0.1 N NaOH/EtOH (5.0 mL, 5.0 mmol). The resulting black suspension was stirred for 45 min, whereupon the flask was attached to a hydrogenator and flushed with H_2. Ethylenediamine (0.67 mL, 10.0 mmol) was added followed by the alcohol **12** (5 g, 15.09 mmol) in anhydrous EtOH (7 mL), and the reaction was stirred until the appropriate amount of H_2 had been taken up. The suspension was poured into Et_2O/pentane (300 mL, 1:1) and filtered through a bed of Fluorosil. The filtrate was concentrated, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:3) to give 4.38 g (87%) of allylic alcohol as a light yellow syrup: ^1H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.36−7.21 (comp, 5 H), 6.50 (d, J = 11.8 Hz, 1 H), 5.70 (dd, J = 9.6, 11.8 Hz, 1 H), 4.53 (dd, J = 6.0, 9.6 Hz, 1 H), 4.03 (d, J = 6.8 Hz, 1 H), 3.86−3.82 (m, 2 H), 1.40 (s, 9 H), 1.39 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 151.4, 136.2, 132.8, 129.9, 128.1, 127.6, 126.4, 92.9, 78.6, 66.1, 63.5, 60.6, 27.6, 25.7, 23.6; IR (neat) ν 3426, 2978, 1695, 1391, 1255, 1172, 1102, 1046 cm^{-1}; mass spectrum (CI) *m*/*z* 334.2021 ($C_{19}H_{27}NO_4$ + H requires 334.2018), 260, 234, 220, 202.

***cis*-[4*S*,4(1′*R*)]-4-[1′-Diazoacetic acid (3′-phenyl-2′-propenyl) ester]-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (16).** To an ice-cooled solution of the above allylic alchohol (490 mg, 1.47 mmol) were added the *p*-toluenesulfonyl hydrazone of glyoxylic acid chloride (645 mg, 2.47 mmol) and *N*,*N*-dimethylaniline (3.2 mL, 2.5 mmol). After 15 min, Et_3N (1.1 mL, 8.1 mmol) was added, and the orange slurry was stirred for 10 min at 0 °C and for 15 min at room temperature. The solvent was removed under reduced pressure and the residue dissolved in EtOAc/hexanes (1:3, 20 mL) and washed once with 20% saturated aqueous Citric acid (5 mL). The organics were dried ($MgSO_4$), and concentrated, and the crude orange residue was purified via flash chromatography eluting with EtOAc (1:5) to give 516 mg (87%) of **16** as a yellow oil: ^1H NMR (300 MHz, DMSO-d_6, rotamers) δ 7.60−7.20 (comp, 5 H), 6.64 (t, J = 12.2 Hz, 1 H), 6.15−6.13 (m, 1 H), 5.62−5.49 (m, 1 H), 4.67 (br s, 1 H), 4.19 (br s, rotamer a, 0.5 H), 4.01 (m, rotamer b, 0.5 H), 3.91 (br s, 2 H), 1.60−1.05 (comp, 15 H); ^{13}C NMR (75 MHz, DMSO-d_6, rotamers) δ 152.7, 151.7, 135.9, 134.0, 133.8, 128.8, 128.5, 127.5, 126.8, 94.6, 93.9, 80.3, 71.0, 70.3, 64.0, 59.2, 46.3, 28.3, 28.1, 26.4, 25.5, 24.3, 23.2; IR ($CDCl_3$) ν 3085, 2979, 2936, 2880, 2112, 1704, 1391, 1242, 1175, 1081 cm^{-1}; mass spectrum (CI) *m*/*z* 402.2030 ($C_{21}H_{27}N_3O_5$ + H requires 402.2029), 316, 302, 288, 274, 260, 246, 230, 216, 202 (base).

***trans*-[4*S*,4(1′*S*)]-4-(1′-Hydroxy-3′-phenyl-2′-propenyl)-2,2-dimethyloxzolidine-3-carboxylic Acid *tert*-Butyl Ester (25a).** To a solution of Red-Al (0.94 mL, 3.28 mmol) in anhydrous Et_2O (2 mL) at 0 °C was added a solution of **13** (680 mg, 2.05 mmol) in Et_2O (0.6 mL) dropwise. After 10 min, the cooling bath was removed, and the reaction was stirred at room temperature for 45 min. A saturated solution of NH_4Cl (0.7 mL) was slowly added (*Caution*! very exothermic). The resulting white slurry was diluted with Et_2O (5 mL), 1 N NaOH (1 mL), and water (1 mL), and the layers were separated. The aqueous phase was re-extracted with Et_2O (2 × 5 mL), and the combined organics were dried ($MgSO_4$) and concentrated. The residue was purified via silica gel chromatography eluting with 30% EtOAc/hexanes to afford 532 mg (78%) of **25a** as clear oil: ^1H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.37−7.20 (comp, 5 H), 6.52 (d J = 15.9 Hz, 1 H), 6.22 (dd, J = 6.9, 15.9 Hz, 1 H), 4.97 (d, J = 4.5 Hz, 1 H), 4.59−4.56 (m, 1 H), 4.05 (dd, J = 2.0, 9.2 Hz, 1 H), 4.00−3.98 (m, 1 H) 3.91 (dd, J = 6.6, 9.1 Hz, 1 H) 1.46 (s, 6 H), 1.39 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 151.3, 136.6, 130.0, 129.3 128.1, 126.7, 93.1, 78.8, 69.8, 62.5, 60.7, 27.7, 25.6, 23.2; IR (neat) ν 3424, 2978, 1694, 1390, 1255, 1172, 1100 cm^{-1}; mass spectrum (CI) *m*/*z* 334.2014 ($C_{19}H_{27}NO_4$ + H requires 334.2018), 316, 260 (base), 216, 202.

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

***trans*-[4*S*,4(1′*S*)]-4-[1′-Diazoacetic acid (3′-phenyl-2′-propenyl) ester]-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (26a).** Prepared in 90% yield as a yellow oil from **25a** by the procedure described for **16**: ^{1}H NMR (500 MHz, DMSO-d_6, rotamers) δ 7.40−7.00 (comp, 5 H), 6.72−6.61 (m, 1 H), 6.24−6.21 (m, 1 H), 5.92−5.84 (m, 1 H), 4.77−3.90 (m, 3 H), 1.65−1.25 (comp, 15 H); ^{13}C NMR (125 MHz, DMSO-d_6, rotamers) δ 155.2, 136.5, 135.7, 134.0, 133.8, 133.7, 129.7, 128.6, 128.4, 128.1, 128.0, 127.4, 126.4, 126.0, 123.7, 98.5, 93.5, 79.4, 77.9, 73.3, 70.9, 63.6, 63.2, 47.4, 45.9, 29.0, 28.0, 25.5, 22.6, 19.0; IR ($CDCl_3$) ν 2978, 2112, 1702, 1376, 1238, 1174, 1092 cm^{-1}; mass spectrum (CI) *m*/*z* 402.2027 ($C_{21}H_{27}N_3O_5$ + H requires 402.2029), 316, 276, 260 (base), 220, 202.

***cis*-[4*S*,4(1′*S*)]-4-(1′-Hydroxy-3′-phenyl-2′-propenyl)-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (25b).** Prepared in 87% as a white solid after recrystallization from EtOAc/hexanes from **13** by the same procedure described for the semi-hydrogenation of **12**: mp 97−99 °C; ^{1}H NMR (500 MHz, DMSO-d_6; 85 °C) δ 7.33−7.22 (comp, 5 H), 6.58 (d, J = 11.8 Hz, 1 H), 5.73 (dd, J = 10.0, 11.8 Hz, 1 H), 4.86−4.14 (m, 2 H), 4.15 (d, J = 9.1 Hz, 1 H), 3.00−2.48 (comp, 2 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.28 (br s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 151.3, 136.3, 131.3, 130.8, 128.0, 127.5, 126.4, 93.0, 78.6, 64.4, 62.4, 60.8, 27.4, 25.8, 22.9; IR ($CDCl_3$) ν 3440, 2977, 1666, 1390, 1255, 1172, 1062 cm^{-1}; mass spectrum (CI) *m*/*z* 334.2024 ($C_{19}H_{27}NO_4$ + H requires 334.2018), 316, 278, 260, 220, 202.

***cis*-[4*S*,4(1′*S*)]-4-[1′-Diazoacetic acid (3′-phenyl-2′-propenyl) ester]-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (26b).** Prepared from **25b** by the same procedure described for **16** in 90% yield as a yellow oil: ^{1}H NMR (500 MHz, toluene-d_8) δ 7.34−6.96 (comp, 5 H), 6.55 (d, J = 11.8 Hz, 1 H), 6.39 (dd, J = 5.1, 10.2 Hz, 1 H), 5.70 (dd, J = 10.6, 10.8 Hz, 1 H), 4.00 (m, 2 H), 3.95 (d, J = 9.4 Hz, 1 H), 3.63 (dd, J = 6.4, 9.4 Hz, 1 H), 1.65 (s, 3 H), 1.41 (s, 3 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, toluene-d_8) δ 164.9, 152.3, 137.7, 129.3, 128.8, 127.8, 126.2, 125.5, 80.1, 70.4, 64.0, 60.0, 45.6, 28.6, 23.7, 20.9; IR ($CDCl_3$) ν 2978, 2111, 1698, 1376, 1173 cm^{-1}; mass spectrum (CI) *m*/*z* 402.2024 ($C_{21}H_{27}N_3O_5$ + H), 316, 260 (base), 202.

General Method for the Cyclopropanation of 16 and 26a,b. To a refluxing solution of Rh_2[(5*R*)-MEPY]$_2$ (0.01 equiv) in CH_2Cl_2 (0.05 M) was added a solution of the diazoester (1 equiv) in CH_2Cl_2 (0.05 M) via syringe pump over 16−20 h. Alternatively, a solution of Cu(TBS)$_2$ (0.02 equiv) in toluene (0.05 M) was added a solution of the diazoester (1 equiv) in toluene (0.05 M) via syringe pump over 16−20 h. The reaction was cooled to room temperature, volatiles were removed under reduced pressure, and the residue was purified by flash chromatography and recrystallization if necessary.

[1*S*,4*S*,5*R*,6*S*,4(4′*S*)]-4′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)-2′,2′-dimethyloxazolidine-3′-carboxylic Acid *tert*-Butyl Ester (17). Obtained in 67% yield from **16** via Rh_2[(5*R*)-MEPY]$_2$-catalyzed cyclization as per the general procedure described above. This isomer was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give **17** as a white solid after recrystallization from EtOAc/hexanes: mp 165−168 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.36−7.24 (comp, 5 H), 4.26 (d, J = 4.5 Hz, 1 H), 4.11 (ddd, J = 1.9, 4.5, 6.3 Hz, 1 H), 4.00 (dd, J = 6.3, 9.6 Hz, 1 H), 3.85 (dd, J = 1.9, 9.6 Hz, 1 H), 2.86 (app t, J = 8.5 Hz, 1 H), 2.68−2.62 (comp, 2 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 172.9, 151.2, 133.0, 128.7, 128.2, 127.0, 93.3, 78.4, 75.2, 27.6, 25.7, 25.3, 25.0, 23.3, 23.1; IR ($CDCl_3$) ν 2979, 2935, 1770, 1694, 1366, 1169 cm^{-1}; mass spectrum (CI) *m*/*z* 275.1300 ($C_{16}H_{18}O_4$ + H requires 275.1283), 259, 217, 199, 171.

[1*R*,4*S*,5*S*,6*S*,4(4′*S*)]-4′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)-2′,2′-dimethyloxazolidine-3′-carboxylic Acid *tert*-Butyl Ester (27a). Obtained in 71% yield via the Cu(TBS)$_2$-catalyzed cyclization of **26a** per the general procedure described above. This isomer was isolated via flash chromatography eluting with EtOAc/hexanes (1:3) as a white solid after recrystallization from EtOAc/hexanes: mp 170−172 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.32−7.13 (comp, 5 H), 4.62 (d, J = 4.7 Hz, 1 H), 4.17 (app t, J = 4.7 Hz, 1 H), 4.01 (dd, J = 6.1, 9.7 Hz, 1 H), 3.95 (dd, J = 1.5, 9.7 Hz, 1 H), 2.66 (dd, J = 4.2, 5.8 Hz, 1 H), 2.46−2.43 (comp, 2 H), 1.54 (s, 3 H), 1.47 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 173.1, 151.7, 137.3, 128.0, 126.3, 93.5, 80.1, 79.5, 63.4, 58.5, 27.5, 27.3, 26.3, 23.0; IR ($CDCl_3$) ν 2980, 1760, 1694, 1365, 1365, 1259, 1176, 1078 cm^{-1}; mass spectrum (CI) *m*/*z* 374.1963 ($C_{21}H_{27}NO_5$ + H requires 374.1967), 318 (base), 302, 274, 260, 200, 174, 144.

[1*R*,4*S*,5*S*,6*R*,4(4′*S*)]-4′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)-2′,2′-dimethyloxazolidine-3′-carboxylic Acid *tert*-Butyl Ester (27b). Obtained in 67% yield from **26b** via Cu(TBS)$_2$-catalyzed cyclization per the general procedure described above. This isomer was isolated via flash chromatography eluting with EtOAc/hexanes (1:3) as a white solid after recrystallization from EtOAc/hexanes: mp 177−179 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.36−7.24 (comp, 5 H), 4.24 (dd, J = 4.4 Hz, 1 H), 4.11 (dd, J = 4.8, 5.0 Hz, 1 H), 4.00 (dd, J = 6.3, 9.7 Hz, 1 H), 3.91 (dd, J = 1.4, 9.7 Hz, 1 H), 2.85 (app t, J = 8.5 Hz, 1 H), 2.72 (dd, J = 6.1, 8.1 Hz, 1 H), 2.63 (dd, J = 6.1, 8.3 Hz, 1 H), 1.53 (s, 3 H), 1.44 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 172.9, 151.4, 133.0, 128.7, 128.1, 126.9, 93.6, 79.4, 75.7, 63.2, 58.0, 27.43, 26.1, 24.9, 24.4, 23.4, 22.7; IR ($CDCl_3$) ν 2982, 1770, 1694, 1366, 1258, 1172, 1085 cm^{-1}; mass spectrum (CI) *m*/*z* 374.1973 ($C_{21}H_{27}NO_5$ + H requires 374.1967).

[1*S*,4*R*,5*R*,6*S*,4(1′*S*)]-[2′-Hydroxy-1′-(4-oxo-3-oxa-6-phenylbicyclo[3.1.0]hex-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester. Compound **17** (869 mg, 2.32 mmol) was dissolved in THF (11 mL) containing concentrated aqueous HCl (1.6 mL) and triethylsilane (370 μL, 2.32 mmol), and the mixture was heated at 70 °C for 6 h. The solvent was removed under reduced pressure, and the crude residue was dissolved in acetonitrile (10 mL). Et_3N (0.4 mL, 2.55 mmol) and Boc_2O (757 mg, 3.48 mmol) were added, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the crude brown residue was purified by silica gel chromatography eluting with 60% EtOAc/hexanes to afford 720 mg (93%) of amino alcohol as a white powdery solid: mp 168−170 °C; ^{1}H NMR (300 MHz, MeOD-d_3) δ 7.89−7.24 (comp, 5 H), 4.25 (d, J = 6.4 Hz, 1 H), 3.78 (ddd, J = 5.0, 5.2, 11.4 Hz, 1 H), 3.63−3.61 (m, 2 H), 2.86 (app t, J = 8.4 Hz, 1 H), 2.69−2.58 (comp, 2 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, MeOD-d_3) δ 176. 7, 158.1, 134.5, 130.6, 129.8, 128.7, 80.6, 77.7, 61.4, 56.2, 28.7, 27.4, 26.7, 25.1; IR (IR card) ν 3382, 2981, 1766, 1682, 1416, 1367, 1169, 982 cm^{-1}; mass spectrum (CI) *m*/*z* 333.1563 ($C_{18}H_{22}NO_5$ + H requires 333.1576), 315, 280 (base), 236.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-[2′-Hydroxy-1′-(4-oxo-3-oxa-6-phenylbicyclo[3.1.0]hex-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester. A solution containing **27a** (3.2 g, 8.5 mmol), triethylsilane (1.4 mL, 8.5 mmol), and 4 N HCl in dioxane (10 mL) was stirred for 1 h. The solvent was removed under reduced pressure, and the crude product was dissolved in CH_3CN (20 mL). Et_3N (1.7 mL, 9.4 mmol) and Boc_2O (2.5 g, 11.3 mmol) were added, and the mixture was stirred at room temperature for 12 h. Solvent was removed under reduced pressure, and the residue was purified via silica gel chromatography eluting with EtOAc/hexanes (1:1) to give 2.61 g of the amino alcohol (92%) as a colorless solid: mp 55−56 °C; ^{1}H NMR (300 MHz, MeOD-d_3) δ 7.33−7.02 (comp, 5 H), 5.07 (d, J = 8.9 Hz, 1 H), 4.79 (s, 1 H), 4.13−4.03 (m, 1 H), 3.84−3.69 (m, 2 H), 2.72−2.28 (m, 2 H), 2.29 (d, J = 4.3 Hz, 1 H), 1.46 (s, 9 H); ^{13}C NMR (300 MHz, MeOD-d_3) δ 174.6, 156.3, 136.8, 128.7, 127.2, 125.9, 81.1, 80.3, 62.1, 54.8, 28.2, 27.4; IR ($CDCl_3$) ν 3333, 2977, 1754, 1693, 1500, 1366, 1171 cm^{-1}; mass spectrum (CI) *m*/*z* 334.1648 ($C_{18}H_{23}NO_5$ + H requires 334.1654), 318, 306, 278 (base), 262, 234, 216, 190, 173.

[1*R*,4*S*,5*S*,6*R*,4(1′*S*)]-[2′-Hydroxy-1′-(4-oxo-3-oxa-6-phenylbicyclo[3.1.0]hex-2-yl)ethyl]carbamic Acid *tert*-Butyl Ester. Prepared in 83% yield as a clear oil after purification by flash chromatography (EtOAc/hexanes: 1:1) from **27b** by the preceding procedure: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.35−7.25 (comp, 5 H), 6.33 (br s, 1 H),

4.51 (dd, J = 5.0, 5.1 Hz, 1 H), 4.23 (d, J = 3.7 Hz, 1 H), 3.75 (ddd, J = 3.7, 5.0, 6.0 Hz, 1 H), 3.44 (dd, J = 5.0, 10.9 Hz, 1 H), 3.43 (dd, J = 5.9, 10.9 Hz, 1 H), 2.77 (dd, J = 8.2, 8.6 Hz, 1 H), 2.69 (ddd, J = 0.7, 6.0, 8.2 Hz, 1 H), 2.52 (ddd, J = 1.0, 6.0, 8.6 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 173.2, 155.2, 133.3, 128.8, 128.0, 126.7, 77.7, 75.6, 59.6, 55.0, 27.7, 25.2, 24.9, 23.2; IR ($CDCl_3$) ν 3372, 1755, 1690, 1515, 1165 cm^{-1}; mass spectrum (CI) m/z 334.1647 ($C_{18}H_{23}NO_5$ + H requires 334.1654), 310, 278 (base), 234.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)aziridine-1-carboxylic Acid *tert*-Butyl Ester (19). DEAD (135 μL, 0.86 mmol) was added dropwise to an ice-cold solution of the corresponding amino alcohol (142 mg, 0.43 mmol) and PPh_3 (173 mg, 0.66 mmol) in THF (6 mL). The cooling bath was removed, and the orange solution was stirred at room temperature for 3.5 h, whereupon the solvent was removed under reduced pressure. The crude orange oily product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 99 mg (74%) of **19** as a clear oil: ^{1}H NMR (300 MHz) δ 7.33−7.26 (comp, 5 H), 3.66 (d, J = 8.0 Hz, 1 H), 2.86−2.83 (m, 2 H), 2.67 (dd, J = 7.1, 7.5 Hz, 1 H), 2.61 (ddd, J = 3.4, 5.9, 8.0 Hz), 2.39 (d, J = 5.9 Hz, 1 H), 2.13 (d, J = 3.4 Hz, 1 H), 1.49 (s, 9 H); ^{13}C NMR (75 MHz) δ 173.5, 161.2, 132.3, 129.3, 128.8, 127.8, 81.9, 77.7, 38.6, 30.7, 27.8, 27.1, 26.4, 23.7; IR ($CDCl_3$) ν 3427, 1770, 1716, 1643, 1308, 1153 cm^{-1}, mass spectrum (CI) m/z 316.1544 ($C_{18}H_{21}NO_4$ + H requires 316.1589), 288, 260 (base), 244, 216, 198, 172, 155.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)aziridine-1-carboxylic Acid *tert*-Butyl Ester (29a). Prepared in 91% yield as clear crystalline plates from the corresponding amino alcohol by same procedure described for **19**: mp 115−117 °C; ^{1}H NMR (300 MHz) δ 7.34−7.05 (comp, 5 H), 4.72 (d, J = 3.0 Hz, 1 H), 2.72 (dt, J = 3.0, 6.0 Hz, 1 H), 2.60 (dd, J = 4.0, 6.0 Hz, 1 H), 2.37−2.31 (comp, 4 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz) δ 173.8, 161.7, 136.9, 128.7, 127.2, 126.0, 81.8, 38.6, 28.5, 28.3, 27.9, 27.8, 26.9; IR ($CDCl_3$) ν 2979, 1780, 1721, 1301, 1160 cm^{-1}; mass spectrum (CI) m/z 316.1530 ($C_{18}H_{21}N_4$ + H requires 316.1549), 300, 288, 260, 216 (base), 199, 187, 170, 155, 143.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)aziridine-1-carboxylic Acid *tert*-Butyl Ester (29b). Prepared in 95% yield from the corresponding amino alcohol by the procedure described for **19**: mp 119−120 °C; ^{1}H NMR (300 MHz) δ 7.36−7.26 (comp, 5 H), 4.32 (d, J = 3.1 Hz, 1 H), 2.78 (dd, J = 8.3, 8.5 Hz, 1 H), 2.70 (comp, 3 H), 1.37 (d, J = 6.3, 1 H), 1.35 (dd, J = 3.5, 3.7 Hz, 1 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz) δ 173.6, 161.6, 132.6, 129.1, 128.7, 127.6, 81.4, 73.4, 38.6, 27.7, 27.6, 26.0, 25.7, 23.4; IR ($CDCl_3$) ν 2980, 1770, 1721, 1306, 1160 cm^{-1}; mass spectrum (CI) m/z 316.1549 ($C_{18}H_{21}NO_4$ + H requires 316.1549), 260, 216 (base), 199.

[1*S*,4*R*,5*R*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)propyl-1′-carbamic Acid *tert*-Butyl Ester (20). A solution of 1.43 M MeLi in Et_2O (120 μL, 0.172 mmol) was added to a slurry of CuBr·DMS (18 mg, 0.086 mmol) in Et_2O (1.3 mL) at 0 °C to give a clear solution. A solution of **19** (14 mg, 0.043 mmol) in CH_2Cl_2 (200 μL) was then added dropwise. The resulting yellow slurry was stirred for 5 min at 0 °C and then for 5 min at room temperature, whereupon saturated NH_4Cl (0.5 mL) containing saturated NH_4OH (1 drop) was added. Et_2O (25 mL) and H_2O (5 mL) were then added and the layers separated. The aqueous layer was extracted with additional Et_2O (2 × 10 mL), the combined organics were dried ($MgSO_4$) and concentrated, and the residue was purified via flash chromatography eluting with EtOAc/hexanes (1:4) to give 13 mg (90%) of **20** as a white solid: mp 181−182 °C; ^{1}H NMR (300 MHz) δ 7.37−7.27 (comp, 5 H), 4.55 (d, J = 9.7 Hz, 1 H), 4.07 (d, J = 4.9 Hz, 1 H), 3.76−3.68 (m, 1 H), 2.78 (dd, J = 8.1, 9.0 Hz, 1 H), 2.60 (ddd, J = 0.9, 6.0, 9.0 Hz, 1 H), 2.48 (dd, J = 6.0, 8.1 Hz, 1 H), 1.81−1.70 (m, 1 H), 1.43 (s, 9 H), 1.39−1.22 (m, 1 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.0, 155.7, 132.4, 129.4, 128.9, 127.8, 79.8, 79.2, 55.4, 28.3, 26.5, 26.2, 24.0, 22.5, 10.1; IR (neat) ν 3386, 2977, 1758, 1693, 1513, 1366, 1173, 975 cm^{-1}; mass spectrum m/z 332.1863 ($C_{19}H_{25}NO_4$ + H requires 332.1862), 304, 276 (base), 260, 243, 232, 215.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)propyl-1′-carbamic Acid *tert*-Butyl Ester (30a). Prepared in 93% yield as a white solid from **29a** according to the procedure described for **20**: mp 181−182 °C; ^{1}H NMR (300 MHz) δ 7.32−7.01 (comp, 5 H), 4.57 (s, 1 H), 4.46 (d, J = 9.4 Hz, 1 H), 3.84 (m, 1 H), 2.70 (dd, J = 4.5, 5.3 Hz, 1 H), 2.26 (d, J = 4.5 Hz, 2 H), 1.67−1.57 (m, 2 H), 1.46 (s, 9 H), 1.01 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.7, 156.2, 137.1, 127.2, 126.0, 82.7, 79.3, 55.5, 29.7, 28.6, 28.3, 28.2, 27.7, 25.1, 10.6; IR ($CDCl_3$) ν 3338, 2970, 2934, 1776, 1704, 1514, 1174 cm^{-1}; mass spectrum (CI) m/z 332.1868 ($C_{19}H_{25}NO_4$ + H requires 332.1862), 316, 304, 276 (base), 260, 232, 215.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-1′-(4-Oxo-3-oxa-6-phenylbicyclo-[3.1.0]hex-2-yl)propyl-1′-carbamic Acid *tert*-Butyl Ester (30b). Prepared in 93% yield as a white solid from **29b** according to the same procedure described for **20**: mp 116−118 °C; ^{1}H NMR (300 MHz) δ 7.33−7.21 (comp, 5 H), 4.47 (d, J = 9.5 Hz, 1 H), 4.10 (d, J = 0.6 Hz, 1 H), 3.79 (ddd, J = 0.6, 6.2, 8.7 Hz, 1 H), 2.67 (d, J = 7.7 Hz, 1 H), 2.66 (d, J = 7.1 Hz, 1 H), 2.50 (dd, J = 7.1, 7.7 Hz, 1 H), 1.51−1.40 (m, 2 H), 1.41 (s, 9 H), 0.87 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.6, 156.3, 132.9, 129.3, 129.0, 128.9, 127.7, 79.7, 79.0, 55.5, 28.3, 26.5, 25.6, 25.2, 23.9, 10.4; IR ($CDCl_3$) ν 3334, 2971, 1764, 1698, 1522, 1173 cm^{-1}; mass spectrum (CI) m/z 332.1871 ($C_{19}H_{25}NO_4$ + H requires 332.1861), 332 (base), 308, 276.

[1*R*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-(1′-Hydroxy-2′-carbamic acid *tert*-butyl ester)butyl-3-phenylcyclopropane-1-*N*-methoxymethylamide. To a slurry of HCl·HN(Me)OMe (1.15 g, 11.7 mmol) in CH_2Cl_2 (50 mL) under argon at 0 °C was added 2.0 M $AlMe_3$ in toluene (6.85 mL, 13.7 mmol). This clear solution was stirred at 0 °C for 10 min, whereupon the cooling bath was removed. Compound **20** (649 mg, 1.96 mmol) in CH_2Cl_2 (16 mL) was added, and the solution was stirred for 12 h. A solution of aqueous sodium phosphate dibasic (6 mL) was added, and the resulting suspension was dissolved in $CHCl_3$ (50 mL) and filtered through a bed of Celite. The filtrate was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography eluting with 60% EtOAc in hexanes to afford 511 mg (66%) of the hydroxy amide as a clear oil that solidified upon standing: mp 103−106 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.27−7.16 (comp, 5 H), 5.44 (br s, 1 H), 3.82 (dd, J = 5.0, 10.0 Hz, 1 H), 3.67 (s, 3 H), 3.46 (ddd, J = 5.0, 9.3, 14.0 Hz, 1 H), 3.14 (s, 3 H), 2.68 (dd, J = 9.5, 10.5 Hz, 1 H), 2.52 (dd, J = 9.0, 9.5 Hz, 1 H), 1.78 (app q, J = 9.2 Hz, 1 H), 1.63 (m, 1 H), 1.41 (d, J = 2.0 Hz, 1 H), 1.38 (s, 9 H), 1.35−1.29 (m, 1 H), 0.80 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 173.0, 155.4, 136.0, 129.2, 127.7, 125.9, 77.22, 68.8, 60.9, 56.5, 28.1, 27.7, 22.1, 20.5, 10.6; IR (neat) ν 3433, 2971, 1710, 1633, 1499, 1454, 1391, 1365, 1172 cm^{-1}; mass spectrum (CI) m/z 393.2381 ($C_{21}H_{32}N_2O_5$ + H requires 393.2389), 393, 337 (base), 319, 234.

[1*R*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-(1′-*tert*-Butyldimethylsilanyloxy-2′-carbamic acid *tert*-butyl ester)butyl-3-phenylcyclopropane-1-*N*-methoxymethylamide (21). To a solution of the hydroxy amide (84 mg, 0.21 mmol) from the preceding reaction in CH_2Cl_2 (1 mL) at −78 °C were added 2,6-lutidine (50 μL, 0.43 mmol) and TBDMSOTf (79 μL, 0.34 mmol). The solution was stirred for 4 h at −78 °C, whereupon H_2O (100 μL) was added, and the solution was allowed to warm to room temperature. $CHCl_3$ (10 mL) was added, and the solution was dried (Na_2SO_4), filtered, and concentrated. The residue was purified via column chromatography eluting with EtOAc/hexanes (1:10) to give 105 mg (99%) of **21** as a light yellow oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.30−7.12 (comp, 5 H), 5.03 (dd, J = 3.3, 9.5 Hz), 4.88 (br s, 1 H), 3.60 (s, 3 H), 3.31−3.28 (m, 1 H), 3.00 (s, 3 H), 2.69 (app t, J = 9.8 Hz, 1 H), 2.61 (dd, J = 8.7, 9.8 Hz, 1 H), 1.73 (ddd, J = 8.7, 9.5, 9.8 Hz, 1 H), 1.72−1.65 (m, 1 H), 1.43−1.35 (m, 1 H), 1.35 (s, 9 H), 0.89 (s, 9 H), 0.80 (t, J = 7.4 Hz, 1 H), 0.11 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 170.0, 154.7, 136.0, 129.5, 127.6, 125.8, 77.4, 68.2, 61.0, 55.9, 32.2, 30.1, 28.4, 28.1, 27.9, 25.9, 25.4, 20.8, 20.1, 18.0, 10.8, −4.1, −5.1; IR (neat) ν

2931, 1717, 1660, 1498, 1497, 1251, 1171, 1094, 836 cm^{-1}; mass spectrum (CI) *m/z* 507.3258 ($C_{27}H_{46}N_2O_5Si$ + H requires 507.3254), 491, 449, 433, 375, 348, 319 (base).

[1*S*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-(1′-*tert*-Butyldimethylsilanyloxy-2′-carbamic acid *tert*-butyl ester)butyl-3-phenylcyclopropane-1-carboxylic Acid (22). To a solution of **21** (48 mg, 0.10 mmol) in Et_2O (1 mL) at 0 °C was added solid KO^{t}Bu (64 mg, 0.57 mmol) in one portion. The solution was stirred for 2 h at 0 °C, whereupon H_2O (40 μL) was added. This biphasic mixture was diluted with EtOAc (5 mL) and washed once with saturated aqueous citric acid (0.5 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated, and the crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to afford 43 mg (97%) of **22** as a clear oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.31−7.14 (comp, 5 H), 6.09 (d, *J* = 8.8 Hz, 1 H), 3.15 (comp, 2 H), 2.61 (dd, *J* = 5.4, 9.8 Hz, 1 H), 2.12 (dd, *J* = 4.3, 5.2 Hz, 1 H), 1.95−1.91 (m, 1 H), 1.33 (s, 9 H), 1.22−0.87 (comp, 2 H), 0.84 (s, 9 H), 0.56 (t, *J* = 7.4 Hz, 3 H), 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 178.5, 174.1, 155.2, 136.0, 128.2, 127.9, 126.5, 99.4, 77.1, 71.6, 56.1, 32.1, 31.2, 28.2, 25.7, 24.1, 22.6, 17.7, 10.7, −4.3, −4.6; IR (neat) ν 3248, 2930, 1707, 1651, 1462, 1405, 1255, 1172, 1097, 836, 773 cm^{-1}; mass spectrum (CI) *m/z* 464.2827 ($C_{25}H_{41}NO_5Si$ + H requires 464.2832), 408, 350 313, 276 (base).

[1*S*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-(1′-*tert*-Butyldimethylsilanyloxy-2′-carbamic acid *tert*-butyl ester)butyl-3-phenylcyclopropane-1-carboxyl-L-methionine Methyl Ester. A solution of the acid **22** (204 mg, 0.44 mmol) and HOBt (190 mg, 1.41 mmol) in DMF (3.4 mL) was cooled to −10 °C (NaCl/ice) and stirred for 20 min. In a separate flask was prepared MetOMe via treatment of a solution of HCl·MetOMe (176 mg, 0.88 mmol) in DMF (1 mL) with Et_3N (124 μL, 0.88 mmol). The amine component was then transferred to the acid solution via syringe, EDC (135 mg, 0.70 mmol) was added, and the reaction was stirred at room temperature overnight. The solution was partitioned between EtOAc (9 mL), brine (4 mL) and saturated citric acid (4 mL). The layers were separated, and the organic phase was washed with saturated $NaHCO_3$ (4 mL) and brine (4 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude yellow product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to afford 233 mg (87%) of the tripeptide as a white solid: mp 61−64 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 8.44 (d, *J* = 7.8 Hz, 1 H), 7.32−7.19 (comp, 5 H), 5.22 (br s, 1 H), 4.48 (dt, *J* = 3.2, 5.5 Hz, 1 H), 3.62 (s, 3 H), 3.27 (dd, *J* = 3.9, 9.9 Hz, 1 H), 3.13−3.06 (m, 1 H), 2.57−2.42 (comp, 3 H), 2.05 (s, 3 H), 2.02−1.83 (comp, 2 H), 1.32 (s, 9 H), 1.26−1.19 (m, 2 H), 0.86 (s, 9 H), 0.66 (t, *J* = 7.3 H, 3 H), 0.11 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 172.5, 171.5, 155.2, 136.85, 128.1, 128.0, 126.3, 77.0, 71.5, 56.1, 52.0, 50.8, 30.7, 30.5, 29.4, 28.2, 25.8, 24.6, 22.5, 17.7, 14.4, 10.7, −4.3, −4.6; IR ($CDCl_3$) ν 3304, 2956, 1722, 1680, 1650, 1538, 1499, 1355, 1255, 1171 cm^{-1}; mass spectrum (CI) *m/z* 609.3388 ($C_{31}H_{52}N_2O_6SiS$ + H requires 609.3394), 537, 509, 495, 451, 421 (base), 232, 117.

[1*R*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-L-dimethylthiazolidine)carbamate]-1′-hydroxy]butyl-3-phenylcyclopropane-1-carboxyl-L-methionine Methyl Ester (24). The tripeptide (152 mg, 0.25 mmol) from the preceding experiment in 4 N HCl in dioxane (2 mL) was stirred at room temperature for 30 min, whereupon solvent was removed under reduced pressure. The crude deprotected material was dissolved in THF (2 mL) containing Et_3N (30 mg, 0.3 mmol), **23** (28 mg, 0.74 mmol) was added, and the reaction was stirred overnight at room temperature. Solvent was removed under reduced pressure, and the crude residue was purified via flash chromatography eluting with EtOAc/hexanes (1:1) to afford 96 mg (60%) of **24** as a pale yellow oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 8.25 (d, *J* = 7.4 Hz, 1 H), 7.28−7.16 (comp, 5 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 4.59 (dd, *J* = 2.7, 7.1 Hz, 1 H), 4.46−4.44 (m, 1 H), 3.63 (s, 3 H), 3.52−3.49 (m, 1 H), 3.25 (dd, *J* = 7.1, 12.0 Hz, 1 H), 3.05 (dd, *J* = 3.8, 8.3 Hz, 1 H), 2.91 (dd, *J* = 2.7, 12.0 Hz, 1 H), 2.57−2.48 (comp, 3 H), 2.29 (app t, *J* = 5.3 Hz, 1 H), 2.07 (s, 3 H), 2.04−1.90 (comp, 3 H), 1.76 (s, 3 H), 1.75−1.71 (m, 1 H), 1.71 (s, 3 H), 1.54−1.51 (m, 1 H), 1.33 (s, 9 H), 0.78 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.7, 171.2, 169.2, 151.3, 136.4, 127.9, 127.5, 125.6, 79.3, 70.4, 69.5, 66.2, 54.3, 51.2, 51.0, 30.8, 30.2, 29.9, 29.3, 28.9, 28.8, 27.7, 27.5, 24.2, 21.5, 14.2, 10.0; IR ($CDCl_3$) ν 3305, 2974, 2932, 1742, 1658, 1530, 1445, 1347, 1168, 757 cm^{-1}; mass spectrum (CI) *m/z* 638.2931 ($C_{31}H_{47}N_3O_7S_2$ + H requires 638.2934), 621, 591, 567, 538 (base), 302, 246, 231, 203, 161, 117.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-4-[1′-L-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]ethyl-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (32a). The lactone **30a** (170 mg, 0.52 mmol) was taken up in 4 N HCl/dioxane (6 mL) and stirred with heating for 30 min. Excess HCl was removed by bubbling a stream of argon through the solvent, and the mixture was then concentrated in vacuo. The crude oily residue was triturated with Et_2O (2×) and dried in vacuo to give the deprotected amine salt. This material was taken up in CH_2Cl_2 (4 mL) and DMF (0.4 mL), treated with Et_3N (72 μL, 0.73 mmol), and cooled to 0 °C. HOBt (70 mg, 0.52 mmol) and **31** (136 mg, 0.52 mmol) were then added, and the reaction was stirred for 3 h. The mixture was filtered, and the filtrate was washed with 0.1 N HCl (2 × 5 mL), brine (1 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), and again with brine (1 × 5 mL). The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo, and the crude oily product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 240 mg (98%) of **32a** as an oil: ^{1}H NMR (300 MHz) δ 7.30−7.01 (comp, 5 H), 6.26 (br s, 1 H), 4.88 (d, *J* = 6.4 Hz, 1 H), 4.59 (s, 1 H), 4.24 (dd, *J* = 7.9, 14.9 Hz, 1 H), 3.32 (dd *J* = 6.8, 12.4 Hz, 1 H), 3.18 (d, *J* = 12.4 Hz, 1 H), 2.57 (dd, *J* = 4.0, 6.0 Hz, 1 H), 2.37 (br s, 1 H), 2.23 (dd, *J* = 3.2, 3.6 Hz, 1 H), 1.83 (s, 3 H), 1.80 (s, 3 H), 1.76−1.59 (m, 1 H), 1.51 (s, 9 H), 1.02 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 174.2, 171.9, 153.4, 137.1, 128.6, 127.0, 126.1, 82.3, 82.1, 77.2, 71.2, 67.7, 54.2, 30.9, 29.5, 28.9, 28.7, 28.6, 28.4, 27.5, 24.9, 10.5; IR ($CDCl_3$) ν 3317, 2973, 1765, 1693, 1528, 1367, 1172 cm^{-1}; mass spectrum (CI) *m/z* 474.2191 ($C_{25}H_{33}N_2O_5S$ requires 474.2188), 447, 419, 403, 375, 301, 171.

[1*R*,4*S*,5*S*,6*R*,4(1′*S*)]-4-[1′-L-Amino-[*tert*-butyl-(*N*-(*S*)-dimethylthiazolidine)carbamate]ethyl-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (32b). Prepared in 80% yield as a white solid from **30b** according to the procedure described for **32a**: mp 159−161 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.47 (d, *J* = 8.2 Hz, 1 H), 7.34−7.25 (comp, 5 H), 4.79 (d, *J* = 3.2, 7.0 Hz, 1 H), 4.12 (d, *J* = 2.5 Hz, 1 H), 4.02−3.97 (m, 1 H), 3.33 (dd, *J* = 7.0, 12.1 Hz), 2.95 (dd, *J* = 3.2, 12.1 Hz, 1 H), 2.77 (dd, *J* = 8.2, 8.5 Hz, 1 H), 2.57 (dd, *J* = 6.1, 8.2 Hz, 1 H), 2.50 (dd, *J* = 6.1, 8.5 Hz, 1 H), 1.80 (s, 3 H), 1.75 (s, 3 H), 1.56−1.40 (m, 2 H), 1.39 (s, 9 H), 0.87 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 173.2, 170.2, 151.4, 133.2, 128.8, 128.0, 126.8, 79.1, 77.8, 70.4, 65.9, 53.0, 30.7, 29.3, 27.8, 27.6, 25.4, 24.9, 23.4, 22.7, 9.9; IR ($CDCl_3$) ν 3424, 2972, 1766, 1674, 1346, 1172 cm^{-1}; mass spectrum (CI) *m/z* 475.2254 ($C_{25}H_{34}N_2O_5S$ + H requires 475.2267), 419, 375, 225.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane 1-Methyl Ester (33a). To a solution of **32a** (156 mg, 0.33 mmol) in EtOH (2 mL) was added 1 N NaOH (0.49 mL, 0.49 mmol), and the reaction was stirred for 1 h, whereupon solvent was removed in vacuo. The crude solid residue was dissolved in H_2O (5 mL), and the solution was acidified by addition of 1 N $NaHSO_4$ (0.5 mL, 0.5 mmol). The resultant white slurry was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (3 mL), and a solution of CH_2N_2 in Et_2O was added using a flame polished pipet until a yellow endpoint was observed. The excess CH_2N_2 was removed by bubbling argon through the solution through a flame-polished pipet. The solvent was removed via rotary evaporation, and the crude hydroxy ester product was dissolved in CH_2Cl_2 (2.5 mL). The solution was cooled to −78 °C under argon, and 2,6-lutidine (77 μL, 0.66 mmol) and TBDMSOTf (114 μL, 0.50 mmol) were added. The reaction was stirred for 1 h at −78 °C and 1 h at −20 °C, whereupon saturated $NaHCO_3$ (1 mL) was added. The

reaction was warmed to room temperature and diluted with CH_2Cl_2 (4 mL). This layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:5) to give 123 mg (60%) of **33a** as an oil and 42 mg (27%) of the lactone **31a**: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.24−7.14 (comp, 5 H), 6.72 (d, J = 8.8 Hz, 1 H), 4.66 (dd, J = 2.6, 7.0 Hz, 1 H), 4.14 (dd, J = 1.8, 8.5 Hz, 1 H), 3.88 (ddd, J = 1.8, 5.9, 8.5 Hz, 1 H), 3.67 (s, 3 H), 3.20 (dd, J = 7.0, 12.0 Hz, 1 H), 2.86 (dd, J = 2.6, 12.0 Hz, 1 H), 2.45 (dd, J = 5.2, 7.3 Hz, 1 H), 2.01 (dd, J = 5.2, 8.7 Hz, 1 H), 1.89 (ddd, J = 7.3, 8.5, 8.7 Hz, 1 H), 1.74 (s, 3 H), 1.73 (s, 3 H), 1.63−1.58 (m, 1 H), 1.49−1.43 (m, 1 H), 1.36 (s, 9 H), 0.94−0.86 (comp, 12 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.0, 169.3, 151.8, 138.1, 127.6, 126.4, 125.9, 79.8, 70.5, 68.9, 66.4, 55.4, 50.9, 40.0, 34.0, 30.0, 29.0, 28.6, 28.227.5, 27.2, 25.4, 25.3, 25.0, 24.3, 17.3, 10.0, −5.1, −5.4; IR ($CDCl_3$) ν 3428, 2932, 1680, 1501, 1452, 1342, 1170, 1060, 840 cm^{-1}; mass spectrum (CI) m/z 621.3386 ($C_{32}H_{52}N_2O_6SiS$ + H requires 621.3386), 605, 565, 521, 489, 433.

[1*R*,4*S*,5*S*,6*R*,4(1′*S*)]-2-[2′-Amino-[*tert*-butyl(*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane 1-Methyl Ester (33b). Prepared in 79% yield as an oil from **32b** according to the procedure described for **33a**: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.30−7.18 (comp, 5 H), 6.53 (d, J = 9.5 Hz, 1 H), 4.72 (dd, J = 1.8, 7.2 Hz, 1 H), 4.66 (dd, J = 0.9, 9.7 Hz, 1 H), 3.94 (m, 1 H), 3.57 (s, 3 H), 3.38 (dd, J = 7.2, 12.2 Hz, 1 H), 3.01 (dd, J = 1.8, 12.2 Hz, 1 H), 2.61 (dd, J = 9.4, 9.8 Hz, 1 H), 2.19 (dd, J = 8.4, 9.4 Hz, 1 H), 1.86 (ddd, J = 8.4, 9.8, 9.8 Hz, 1 H), 1.47−1.39 (m, 1 H), 1.42 (s, 9 H), 0.89 (s, 9 H), 0.75 (t, J = 7.4 Hz, 3 H), 0.08 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 170.3, 169.7, 151.9, 134.2, 129.3, 127.2, 125.8, 80.1, 70.7, 67.3, 66.8, 54.2, 50.6, 30.2, 30.0, 28.4, 28.2, 28.1, 27.5, 25.6, 25.3, 22.6, 17.6, 9.7, −4.8, −5.3; IR ($CDCl_3$) ν 3424, 2958, 2932, 2858, 1730, 1672, 1510, 1337, 1164 cm^{-1}; mass spectrum (CI) m/z 621.3400 ($C_{32}H_{52}N_2O_6SiS$ + H requires 621.3394), 589, 565, 489, 433.

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane-1-carboxylic Acid (34a). A solution of **33a** (80 mg, 0.13 mmol) in EtOH (0.9 mL) containing 1 N NaOH (0.2 mL, 0.2 mmol) was stirred for 1 h at room temperature, and then the solvent was removed under reduced pressure. The residue was dissolved in H_2O (2 mL), and the resulting solution was acidified with 1 N $NaHSO_4$ (0.21 mL, 0.21 mmol). The mixture was with EtOAc (3 × 1 mL), the combined organic layers were dried (MgSO4) and concentrated, and the crud**e** product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 50 mg (64%) of **34a** as an oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.24−7.13 (comp, 5 H), 6.69 (d, J = 9.0 Hz, 1 H), 4.65 (dd, J = 2.5, 7.0 Hz, 1 H), 4.21 (dd, J = 1.8, 8.4 Hz, 1 H), 3.88 (ddd, J = 1.8, 8.3, 10.1 Hz, 1 H), 3.20 (dd, J = 7.0, 12.0 Hz, 1 H), 2.86 (dd, J = 2.5, 12.0 Hz, 1 H), 2.39 (dd, J = 5.2, 7.2 Hz, 1 H), 1.90 (dd, J = 5.2, 8.7 Hz, 1 H), 1.83 (ddd, J = 7.2, 8.4, 8.7 Hz, 1 H), 1.74 (s, 3 H), 1.73 (s, 3 H), 1.62−1.55 (m, 1 H), 1.50−1.45 (m, 1 H), 1.36 (s, 9 H), 0.91 (s, 9 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.9, 169.2, 151.8, 127.7, 126.4, 125.7, 79.8, 70.5, 68.9, 66.4, 55.4, 33.5, 29.9, 28.6, 27.6, 25.5, 25.3, 24.6, 17.4, 9.9, −4.7, −5.4; IR ($CDCl_3$) ν 3431, 2933, 1694, 1651, 1340, 1167 cm^{-1}; mass spectrum (CI) m/z 607.3231 ($C_{31}H_{50}N_2O_6SiS$ + H requires 607.3237), 551, 507, 419, 375 (base), 171.

[1*R*,4*S*,5*S*,6*R*,4(1′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane-1-carboxylic Acid (34b). A solution of **33b** (34 mg, 0.054 mmol) in EtOH (0.5 mL) containing 1 N NaOH (162 μL, 0.162 mmol) was heated at reflux overnight. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O (2 mL). The solution was acidified with excess 1 N HCl (170 μL, 0.170 mmol), and the resulting mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product mixture was purified via flash chromatography eluting with EtOAc (gradient: 1:3 to 1:1) to give 15 mg (47%) of **34b** as a pale yellow oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 12.0 (br s, 1 H), 7.35−7.17 (comp, 5 H), 6.51 (d, J = 9.6 Hz, 1 H), 4.74 (dd, J = 1.0, 9.7 Hz, 1 H), 4.71 (dd, J = 1.7, 7.2 Hz, 1 H), 3.89 (m, 1 H), 3.38 (dd, J = 7.2, 12.2 Hz, 1 H), 3.00 (dd, J = 1.7, 12.2 Hz, 1 H), 2.53 (dd, J = 9.6, 9.9 Hz, 1 H), 2.08 (dd, J = 8.3, 9.6 Hz, 1 H), 1.83 (s, 3 H), 1.70 (ddd, J = 8.3, 9.7, 9.9 Hz, 1 H), 1.75 (s, 3 H), 1.46−1.39 (m, 1 H), 1.43 (s, 9 H), 0.90 (s, 9 H), 0.73 (t, J = 7.4 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.4, 169.6, 151.8, 134.8, 129.3, 127.1, 125.7, 80.1, 70.7, 67.2, 66.8, 54.3, 30.3, 29.6, 28.4, 28.2, 27.5, 25.7, 25.3, 22.8, 17.8, 9.7, −4.5, −5.4; IR ($CDCl_3$) ν 2932, 1704, 1634, 1520, 1338, 1116 cm^{-1}; mass spectrum (FAB) m/z 607.3231 ($C_{31}H_{50}N_2O_6SiS$ + requires 607.3237), 551, 507, 419, 375 (base).

[1*R*,4*S*,5*S*,6*S*,4(1′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane-1-carboxyl-L-cysteine Methyl Ester (35a). A solution of **34a** (50 mg, 0.08 mmol), HCl·MetOMe (17 mg, 0.08 mmol), and HOBt (11 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) and DMF (0.1 mL) was cooled to 0 °C, whereupon Et_3N (11 μL, 0.08 mmol) and DCC (17 mg, 0.08 mmol) were added. The reaction was stirred for 3 d at room temperature, and the solids were removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc (3 mL). The solution was cooled to 0 °C, and the solids were removed by vacuum filtration. The combined filtrates were washed with 0.1 N HCl (1 × 1 mL), H_2O (1 mL) and brine (1 × 1 mL). The organic layer was then dried ($MgSO_4$) and concentrated, and the residue was purified via flash chromatography eluting with EtOAc/hexanes (1:1) to give 44 mg (71%) of **35a** as an oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 8.40 (d, J = 7.4 Hz, 1 H), 7.24−7.12 (comp, 5 H), 6.63 (d, J = 9.1 Hz, 1 H), 4.62 (dd, J = 2.3, 6.9 Hz, 1 H), 4.25−4.39 (comp, 2 H), 3.86 (ddd, J = 1.3, 8.1, 8.7 Hz, 1 H), 3.65 (s, 3 H), 3.17 (dd, J = 6.9, 12.0 Hz, 1 H), 2.86 (dd, J = 2.3, 12.0 Hz, 1 H), 2.54 (dd, J = 7.3, 7.7 Hz, 1 H), 2.30 (dd, J = 5.2. 7.0 Hz, 1 H), 2.10 (ddd, J = 5.2, 7.7, 8.5 Hz, 1 H), 2.06 (s, 3 H), 1.99−1.87 (m, 2 H), 1.78−1.71 (m, 1 H), 1.74 (s, 3 H), 1.73 (s, 3 H), 1.56−1.43 (m, 2 H), 1.36 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, J = 7.4 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.6, 170.4, 169.1, 151.8, 139.3, 127.5, 126.3, 125.5, 79.8, 70.5, 68.2, 66.5, 55.4, 51.2, 51.1, 33.6, 30.0, 29.3, 28.6, 28.3, 28.2, 27.7, 27.5, 25.5, 24.9, 17.4, 14.0, 9.9, 0.7, −4.6, −5.5; IR ($CDCl_3$) ν 2932, 1743, 1657, 1514, 1343, 1167 cm^{-1}; mass spectrum (CI) m/z 752.3790 ($C_{37}H_{61}N_3O_7SiS_2$ + H requires 752.3798), 694, 652, 620, 450, 307, 225.

[1*R*,4*S*,5*S*,6*R*,4(1′*S*)]-2-[2′-Amino[*tert*-butyl (*N*-(*S*)-dimethylthiazolidine)carbamate]-1′-*tert*-butyldimethylsilanyloxy]butyl-3-phenylcyclopropane-1-carboxyl-L-cysteine Methyl Ester (35b). Prepared as a pale yellow oil in 84% yield from **34b** according to the procedure described for **35a**: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 8.43 (d, J = 7.4 Hz, 1 H), 7.39−7.12 (comp, 5 H), 6.48 (d, J = 9.6 Hz, 1 H), 4.85 (d, J = 9.4 Hz, 1 H), 4.72 (dd, J = 1.6, 7.2 Hz, 1 H), 4.38 (ddd, J = 5.4, 8.0, 8.0 Hz, 1 H), 3.87 (ddd, J = 7.6, 9.4, 9.4 Hz, 1 H), 3.58 (s, 3 H), 3.99 (dd, J = 7.2, 12.2 Hz, 1 H), 3.03 (dd, J = 1.6, 12.2 Hz, 1 H), 2.55−2.45 (m, 2 H), 2.40 (dd, J = 9.7, 9.8 Hz, 1 H), 2.16 (dd, J = 8.5, 9.3 Hz, 1 H), 2.04 (s, 3 H), 1.20−1.86 (m, 1 H), 1.83 (s, 3 H), 1.76 (s, 3 H), 1.71 (ddd, J = 8.5, 9.8, 9.8 Hz, 1 H), 1.43 (s, 9 H), 1.40−1.30 (m, 1 H), 0.87 (s, 9 H), 0.67 (t, J = 7.4 Hz, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.7, 169.9, 169.6, 151.8, 134.9, 129.8, 126.7, 125.3, 80.0, 70.8, 67.0, 66.9, 54.2, 51.1, 50.9, 30.3, 30.2, 29.4, 29.3, 28.3, 28.2, 27.5, 26.7, 25.8, 25.3, 22.8, 17.7, 14.0, 9.6, −4.5, −5.4; IR ($CDCl_3$) ν 3280, 2956, 2930, 2854, 1745, 1655, 1515, 1343, 1254, 1164, 1056 cm^{-1}; mass spectrum (CI) m/z 752.3803 ($C_{37}H_{61}N_3O_7SiS_2$ + H requires 752.3798), 736, 694, 620.

***N*-Boc-L-dimethylthiazolidine-L-ethylglycine Methyl Ester.** A mixture of HCl·AbuOMe (108 mg, 0.70 mmol), Et_3N (98 μL, 0.70 mmol), and the pentaflourophenol ester of *N*-Boc-L-dimethylthiazolidine (433 mg, 1.05 mmol) in THF (3 mL) was stirred for 23 h at room temperature. The solvent was removed

under reduced pressure, and the crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 241 mg (96%) of the dipeptide ester as a clear oil: ^{1}H NMR (300 MHz) δ 4.78 (br s, 1 H), 4.61−4.57 (m, 1 H), 3.75 (s, 3 H), 3.75 (br s, 2 H), 2.05−1.85 (m, 1 H), 1.89 (s, 3 H), 1.80 (s, 3 H), 1.80−1.65 (m, 1 H), 1.48 (s, 9 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.3, 170.3, 153.5, 81.6, 71.0, 67.3, 53.4, 52.2, 30.6, 29.1, 28.6, 28.2, 25.6, 9.1; IR ($CDCl_3$) ν 3425, 3323, 2974, 2935, 1743, 1703, 1517, 1348, 1169 cm^{-1}; mass spectrum (CI) m/z 360.1707 ($C_{16}H_{27}N_2O_5S$ requires 360.1719), 305 (base) 261, 250, 222.

***N*-Boc-L-dimethylthiazolidine-L-ethylglycine Carboxylic Acid (36).** To a solution of the ester from the previous experiment (207 mg, 0.57 mmol) in EtOH (3.8 mL) at 0 °C was added 1 N NaOH (0.74 mL, 0.74 mmol). This mixture was then stirred at room temperature for 24 h, whereupon the solvent was concentrated under reduced pressure. The crude product was dissolved in H_2O (5 mL), the solution was acidified to pH 3 by addition of saturated aqueous $KHSO_4$, and the mixture was extracted with EtOAc (3 × 3 mL). The combined organics were dried ($MgSO_4$) and concentrated to give 185 mg (94%) of the acid which was ≥95% pure by ^{1}H NMR and used without further purification: mp 76−77 °C; ^{1}H NMR (300 MHz, MeOD-d_3) δ 9.12 (br s, 1 H), 7.00 (br s, 1 H), 4.80 (br s, 1 H), 4.59 (dt, J = 5.8, 12.6 Hz, 1 H), 3.33−3.18 (m, 2 H), 2.06−1.83 (m, 2 H), 1.89 (s, 3 H), 1.79 (s, 3 H), 1.46 (s, 9 H), 0.95 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, MeOD-d_3) δ 175.1, 171.3, 153.5, 81.9, 71.0, 67.2, 53.3, 30.6, 28.8. 28.7, 28.1, 25.2, 9.0; IR ($CDCl_3$) ν 3409, 3306, 2975, 1704, 1666, 1535, 1367, 1166 cm^{-1}; mass spectrum (CI) m/z 347.1638 ($C_{15}H_{26}N_2O_5S$ + H requires 347.1640), 319, 291, 275, 247.

***N*-Boc-L-dimethylthiazolidine-L-ethylglycine-L-phenylalanine-L-methionine Methyl Ester (37).** *N*-Boc-phenylalaninemethionine methyl ester (42 mg, 0.10 mmol) was dissolved in 4 N HCl in dioxane (0.8 mL), and the solution was heated for about 5 min. The solvent was removed under reduced pressure, and the oily residue was dissolved in DMF (500 μL). Et_3N (14 μL, 0.10 mmol) was added, and the solution cooled to about −5 to −10 °C in an ice−salt bath. The acid from the preceding experiment (33 mg, 0.10 mmol), HOBt (44 mg, 0.33 mmol), and EDC (24 mg, 0.12 mmol) were then added sequentially, and the resulting mixture was stirred overnight at room temperature. The reaction was then partitioned between EtOAc (2 mL), brine (1 mL), and saturated citric acid (1 mL), and the layers were separated. The organic phase was washed with saturated $NaHCO_3$ (1 mL) and brine (1 mL), dried ($MgSO_4$), and concentrated. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:1) to afford 41 mg (67%) of **37** as a white solid: mp 133−136 °C; ^{1}H NMR (500 MHz, DMSO-d_6; 85 °C) δ 8.03 (d, J = 7.5 Hz, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.24−7.15 (comp, 5 H), 4.66 (dd, J = 3.1, 7.1 Hz, 1 H), 4.62−4.58 (m, 1 H), 4.44−4.40 (m, 1 H), 4.24−4.20 (m, 1 H), 3.63 (s, 3 H), 3.28 (dd, J = 7.1, 12.1 Hz, 1 H), 3.04 (dd, J = 5.5, 14.1 Hz, 1 H), 2.93 (dd, J = 3.1, 12.1 Hz, 1 H), 2.86 (dd, J = 8.4, 14.1 Hz, 1 H), 2.50−2.43 (m, 2 H), 2.04 (s, 3 H), 2.02−1.95 (m, 1 H), 1.89 (ddq, J = 5.7, 8.4, 14.2 Hz, 1 H), 1.79 (s, 3 H), 1.73 (s, 3 H), 1.71−1.67 (m, 1 H), 1.58−1.53 (m, 1 H), 1.35 (s, 9 H), 0.81 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 171.1, 170.4, 169.3, 169.3, 151.3, 128.6, 127.5, 125.7, 79.4, 70.4, 66.1, 53.3, 53.2, 53.1, 51.2, 50.7, 50.6, 37.0, 30.6, 30.5, 30.0, 29.2, 28.8, 27.6, 27.5, 25.0, 14.2, 8.9; IR ($CDCl_3$) ν 3319, 3284, 2974, 2932, 1746, 1704, 1641, 1538, 1353, 1173 cm^{-1}; mass spectrum (CI) m/z 639.2868 ($C_{30}H_{46}N_4O_7S_2$ + H requires 639.2886), 591, 539 (base), 476, 420, 376, 311, 272, 229, 201.

***trans*-(1′*S*,2*S*,2′*S*)-2-Benzylhept-4-enoic Acid (2′-Hydroxy-1′-methyl-2′-phenylethyl)methyl Amide (39).** A solution of 2.46 M *n*-BuLi (1.9 mL, 4.7 mmol) in hexane was added to a solution diisopropylamine (0.7 mL, 5.0 mmol) and LiCl (664 mg, 15.7 mmol) in THF (26 mL) at −78 °C. The reaction was stirred at −78 °C for 30 min, warmed to 0 °C for 5 min, and re-cooled to −78 °C. An ice-cooled solution of **38** (665 mg, 2.24 mmol) in THF was added via a cannula over 3 min. The reaction was stirred for 1 h at −78 °C, warmed to 0 °C for 15 min, to room temperature for 5 min, and re-cooled to 0 °C. A solution of the (*E*)-1-bromo-2-pentene (500 mg, 3.36 mmol) in THF (1 mL) was added, and the reaction was stirred for 2 h at 0 °C. The reaction was partitioned between saturated aqueous NH_4Cl (50 mL) and EtOAc/hexanes (1:1, 100 mL). The layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:3) to give 756 mg (93%) of **39** as an oil. The diastereomeric product ratio was determined to be 14:1 by chiral HPLC (Daicel OD column, *i*-PrOH/hexanes (1:10), retention time (rt) **39** = 24.3 min, room temperature *diast*-**39** = 27.1 min): ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C, rotamers) δ 7.29−7.10 (comp, 10 H), 5.47−5.32 (comp, 2 H), 5.1−4.9 (m, 1 H), 4.63−4.45 (m, 2 H), 3.8 (br s, 1 H), 3.02 (s, 3 H), 2.97−2.58 (comp, 3 H), 2.27−1.92 (comp, 4 H), 0.97−0.45 (comp, 5 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C, rotamers) δ 174.1, 174.0, 142.8, 139.7, 132.9, 132.8, 132.1, 128.4, 128.3, 127.6, 127.5, 127.2, 126.7, 126.3, 125.8, 125.3, 73.7, 73.5, 56.8, 54.5, 42.8, 42.6,37.8, 37.5, 35.0, 34.7, 30.6, 30.5, 29.6, 29.3, 26.5, 24.4, 24.3, 29.6, 19.4, 134.0, 13.4, 13.2, 13.1; IR ($CDCl_3$) ν 3028, 2963, 1614, 1494, 1454, 1408 cm^{-1}; mass spectrum m/z 366.2424 ($C_{25}H_{31}NO_2$ + H requires 366.2433), 348, 258.

(1′*R*,3*R*,5*S*)-3-Benzyl-5-(1′-bromopropyl)dihydrofuran-2-one (40). *N*-Bromosuccinimide (670 mg, 3.76 mmol) was added in portions to a solution of **39** (1.25 g, 3.42 mmol) in a mixture (4:1) of THF/H_2O (20 mL) containing glacial acetic acid (1 mL, 17.1 mmol) at 0 °C. The resulting solution was stirred for 1 h at 0 °C and then heated under reflux for 4 h. The reaction was cooled to room temperature, and a mixture of saturated $NaHCO_3$ (40 mL) was added. The mixture was extracted with EtOAc/hexanes (1:1, 3 × 40 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:7) to provide 807 mg (79%) of an inseparable mixture of **40** as a pale yellow oil that was contaminated with varying amounts (4−13%) of a diastereomeric lactone. For **40**: ^{1}H NMR (300 MHz) δ 7.35−7.18 (comp, 5 H), 4.29 (ddd, J = 5.2, 7.1, 7.9 Hz, 1 H), 3.94 (ddd, J = 3.6, 7.1, 9.2 Hz, 1 H), 3.17 (dd, J = 4.5, 13.6 Hz, 1 H), 3.05 (dddd, J = 4.5, 7.0, 8.8, 9.4 Hz, 1 H), 2.82 (dd, J = 8.8, 13.6), 2.27 (ddd, J = 5.2, 9.4, 13.6 Hz, 1 H), 2.16 (ddd, J = 7.0, 7.9, 13.6 Hz, 1 H), 1.96 (ddq, J = 3.6, 7.3, 14.6 Hz, 1 H), 1.73 (ddq, J = 7.3, 9.2, 14.6 Hz, 1 H), 1.04 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 177.8, 137.8, 128.9, 128.7, 126.9, 79.3, 59.3, 41.0, 36.8, 30.7, 27.8, 11.5; IR ($CDCl_3$) ν 2970, 1774, 1454, 1171, 1020 cm^{-1}; mass spectrum (CI) m/z 297.0493 ($C_{14}H_{17}O_2Br$ + H requires 297.0490), 217, 199, 171, 148.

(1′*S*,3*R*,5*S*)-5-(1′-Azidopropyl)-3-benzyldihydrofuran-2-one. A suspension of sodium azide (114 mg, 1.75 mmol) and **40** (260 mg, 0.87 mmol) in DMF (3 mL) was heated at 50 °C overnight. The mixture was cooled to room temperature and partitioned between H_2O (8 mL) and a mixture (1:1) of EtOAc/hexanes (16 mL). The layers were separated, and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified via flash chromatography eluting with EtOAc/hexanes (1:10) to give 159 mg (70%) of the desired azide as a light yellow oil that was contaminated with about 5% of an inseparable and unidentified isomer: ^{1}H NMR (300 MHz) δ 7.35−7.19 (comp, 5 H), 4.28 (ddd, J = 3.9, 5.1, 9.0 Hz, 1 H), 3.22−3.15 (comp, 2 H), 3.09 (ddd, J = 4.7, 8.0, 9.0 Hz), 2.79 (dd, J = 9.0, 13.6 Hz, 1 H), 2.10 (ddq, J = 5.0, 9.0, 14.5 Hz, 1 H), 1.68 (ddq, J = 7.4, 7.4, 14.5 Hz, 1 H), 1.02 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz) δ 177.9, 137.9, 128.9, 128.8, 128.7, 126.9, 126.8, 78.4, 76.6, 66.4, 65.8, 40.7, 36.9, 29.9, 23.5, 10.5; IR ($CDCl_3$) ν 2968, 2931, 2105, 1775, 1152 cm^{-1}; mass spectrum (CI) m/z 260.1398 ($C_{14}H_{17}N_3O_2$ + H requires 260.1399), 232, 177, 131.

(1′*S*,3*R*,5*S*)-[1-[4′-Benzyl-5-oxotetrahydrofuran-2′-yl]-1-[8′*S*-(*tert*-butyloxycarbonyl)dimethylthiazolidine]-ethyl]carboxamide (41). A suspension of the azide (58 mg, 0.22 mmol) from the previous reaction and 10% Pd/C in dry MeOH (1.2 mL) was stirred under an atmosphere of H_2 (1 atm) for 4 h, whereupon the catalyst was removed by filtration through a plug of Celite. The filtrate was concentrated under reduced pressure, and the resultant crude amine was dissolved

in THF (1.1 mL). Diisopropylethylamine (38 μL, 0.22 mmol) and BocDMTOPfp (90 mg, 0.22 mmol) were added, and the reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the crude oily product was purified via flash chromatography eluting with EtOAc/hexanes (1:1) to give 85 mg (81%) of pure **41** as a white foam: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.30−7.19 (comp, 6 H), 4.74 (dd, J = 2.9, 7.0 Hz, 1 H), 4.43 (ddd, J = 3.6, 5.3, 8.3 Hz, 1 H), 3.81 (ddd, J = 3.6, 5.0, 9.1), 3.30 (dd, J = 7.0, 12.1 Hz, 1 H), 3.01 (dd, J = 5.0, 13.8 Hz, 1 H), 2.91 (dddd, J = 5.0, 7.4, 9.2, 9.7 Hz, 1 H), 2.88 (dd, J = 2.9, 12.1 Hz, 1 H), 2.73 (dd, J = 9.2, 13.8 Hz, 1 H), 2.04 (ddd, J = 5.3, 9.7, 13.2 Hz, 1 H), 1.98 (ddd, J = 7.4, 8.3, 13.2 Hz, 1 H), 1.76 (s, 3 H), 1.73 (s, 3 H), 1.56 (ddd, J = 5.0, 7.4, 13.8 Hz, 1 H), 1.45 (ddd, J = 7.4, 9.1, 13.8 Hz, 1 H), 1.38 (s, 9 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 177.4, 170.1, 151.5, 138.1, 128.3, 127.8, 125.9, 79.3, 78.6, 70.3, 66.1, 52.8, 35.7, 30.5, 29.2, 28.7, 27.7, 27.6, 23.7, 9.8; IR ($CDCl_3$) ν 3310, 2972, 2933, 1770, 1662, 1345, 1166 cm^{-1}; mass spectrum (CI) m/z 476.2333 ($C_{25}H_{36}N_2O_5S$ requires 476.2345), 449, 421, 405, 377.

(2*R*,4*S*,5*R*)-5-[L-(*tert*-Butyloxycarbonyl)dimethylthiazolidinecarboxamide]-4-[(*tert*-butyldimethysilyl)oxy-2-(phenylmethyl)]heptanoic Acid (42). The lactone **41** (343 mg, 0.72 mmol) was dissolved in a mixture (2:1) of dioxane/H_2O (6 mL), and 1 N NaOH (0.8 mL, 0.8 mmol) was added. The reaction was stirred for 2 h at room temperature, and solvent was concentrated to one-half its original volume under reduced pressure. The resulting solution was acidified with 1 N $NaHSO_4$ (10 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the crude hydroxy acid was dissolved in DMF (5 mL) under argon. Imidazole (466 mg, 6.84 mmol) and TBSCl (543 mg, 3.60 mmol) were added, and the reaction was stirred overnight at room temperature. MeOH (1 mL) was added, and the reaction was stirred for an additional 1 h, whereupon the solvent was removed under reduced pressure. The resulting solution was poured into ice-cold H_2O (50 mL), and the mixture acidified to pH 3 by addition of 1 N $NaHSO_4$ (30 mL). This mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:1) to afford 321 mg (73%) of **42** as a clear oil: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.27 (comp, 5 H), 6.82 (d, J = 9.0 Hz, 1 H), 4.69 (dd, J = 3.2, 7.1 Hz, 1 H), 3.75 (ddd, J = 2.5, 4.7, H), 3.67 (dddd, J = 2.5, 4.6, 7.3, 9.0 Hz, 1 H), 3.29 (dd, J = 7.1, 12.1 Hz, 1 H), 3.01−2.98 (m, 1 H), 2.88 (dd, J = 9.8, 15.9 Hz, 1 H), 2.72−2.67 (comp, 2 H), 1.81−1.78 (m, 1 H), 1.51 (ddd, J = 4.6, 7.4, 13.7 Hz, 1 H), 1.47−1.42 (m, 1 H), 1.40 (s, 9 H), 1.30 (ddd, J = 7.4, 7.4, 13.7 Hz, 1 H), 0.86 (s, 9 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 175.2, 169.6, 151.5, 138.8, 128.2, 127.6, 125.6, 79.5, 70.8, 70.5, 66.2, 53.9, 42.8, 37.l9, 34.6, 32.8, 30.4, 28.7, 28.0, 27.6, 25.4, 22.3, 17.2, 10.3, −5.0, −5.1; IR ($CDCl_3$) ν 2931, 1709, 1342, 1254, 1167, 1065 cm^{-1}; mass spectrum (FAB) m/z 609.3400 ($C_{31}H_{50}N_2O_6SiS$ + H requires 609.3394), 553, 509 (base), 491, 451, 377.

(2*R*,4*S*,5*R*)-1-(L-Methionine methyl ester)-5-[L-(*tert*-butyloxycarbonyl)dimethylthiazolidinecarboxamide]-4-[(*tert*-butyldimethysilyl)oxy-2-(phenylmethyl)]heptanamide (43). A solution of the acid **42** (93 mg, 0.15 mmol), the hydrochloride salt of methionine methyl ester (32 mg, 0.16 mmol), and HOBt (22 mg, 0.16 mmol) in a mixture (10:1) of CH_2Cl_2/DMF (550 μL) was cooled to 0 °C, and Et_3N (22 μL, 0.16 mmol) was added. After 5 min, DCC (33 mg, 0.16 mmol) was added, and the reaction was stirred overnight at room temperature. The precipitated solids were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and cooled to 0 °C. The precipitated solids were again removed again by filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography eluting with EtOAc/hexanes (1:4) to give 94 mg (82%) of **43** as a white foam: ^{1}H NMR (500 MHz, DMSO-d_6, 85 °C) δ 7.78 (d, J = 7.5 Hz, 1 H), 7.26−7.15 (comp, 5 H), 6.69 (d, J = 8.9 Hz, 1 H), 4.70 (dd, J = 2.6, 7.0 Hz, 1 H), 4.36 (ddd, J = 5.5, 9.1, 9.1 Hz, 1 H), 3.68 (ddd, J = 2.0, 5.0, 7.2, 9.0 Hz, 1 H), 3.63 (ddd, J = 2.0 Hz, 6.0, 6.0 Hz, 1 H), 3.60 (s, 3 H), 3.31 (dd, J = 7.1, 12.1 Hz, 1 H), 3.07 (dd, J = 2.6, 12.1 Hz), 2.93 (dd, J = 6.8, 13.8 Hz, 1 H), 2.71 (dddd, J = 6.8, 6.8, 7.4, 8.0 Hz, 1 H), 2.58 (dd, J = 7.4, 13.8 Hz, 1 H), 2.48 (m, 1 H), 2.04 (s, 3 H), 2.00−1.85 (m, 2 H), 1.81 (dddd, J = 5.8, 8.0, 13.8 Hz), 1.78 (s, 3 H), 1.74 (s, 3 H), 1.46−1.29 (comp, 3 H), 1.40 (s, 9 H), 0.85 (s, 9 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.03 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 85 °C) δ 173.6, 171.5, 169.6, 151.6, 139.1, 128.3, 127.5, 125.4, 79.6, 71.3, 70.4, 66.4, 53.8, 51.1, 50.8, 43.4, 38.1, 35.0, 30.5, 30.3, 29.4, 28.7, 28.0, 27.6, 25.4, 23.2, 17.2, 14.1, 10.2, −4.9, −5.1; IR ($CDCl_3$) ν 3421, 3316, 2929, 2853, 1743, 1657, 1518, 1340, 1166 cm^{-1}; mass spectrum (CI) m/z 754.3948 ($C_{37}H_{63}N_3O_7SiS_2$ + H requires 754.3955), 698, 654, 452, 225.

L-Cysteine-L-ethylglycine-L-phenylalanine-L-methioninecarboxylic Acid Trifluoroacetate Salt (6). To a solution of **24** (56 mg, 0.088 mmol) in MeOH (2.5 mL) and THF (1.3 mL) was added 1 M LiOH (110 μL, 0.110 mmol), and the mixture was stirred for 18 h at room temperature. The solvent was removed, and the crude product was dissolved in H_2O (1.0 mL). The solution was acidified with 1 N HCl (110 μL) and extracted with EtOAc (3 × 1 mL). The combined EtOAc layers were dried ($MgSO_4$) and concentrated to give 45 mg (82%) of crude *N*-Boc acid that was dissolved in CF_3CO_2H/CH_2Cl_2 (4:1.3 mL), and the solution was stirred for 2 h under argon. The solvent was removed, and the crude acetonide was triturated with Et_2O/pentane (1:1, 2 × 1 mL). The solid residue was dissolved in a mixture of MeOH/H_2O (67 mL; 67 mL), and the solvents were removed under reduced pressure (bath temperature 50 °C). This process was repeated twice to complete the hydrolysis of the *N*-terminal *N*,*S*-acetal, and the crude product was purified by reverse phase chromatography [HPLC t_R 6min (25% CH_3CN/74.9% H_2O/0.1% CF_3CO_2H)] to give 7 mg (17%) of **6** as an oil: ^{1}H NMR (500 MHz, MeOD-d_3) δ 7.26−7.15 (comp, 5 H), 4.65 (dd, J = 5.6, 8.4 Hz, 1 H), 4.53 (dd, J = 4.5, 9.2 Hz, 1 H), 4.25 (dd, J = 5.6, 8.4 Hz), 4.00 (t, J = 5.8 Hz, 1 H), 3.15 (dd, J = 5.6, 14.0 Hz, 1 H), 2.93 (dd, J = 8.6, 14.0 Hz, 1 H), 2.94 (d, J = 5.9 Hz, 2 H), 2.54 (ddd, J = 5.2, 8.8, 13.6 Hz, 1 H), 2.47 (ddd, J = 7.3, 8.5, 13.6 Hz, 1 H), 2.16−2.09 (m, 1 H), 2.07 (s, 3 H), 1.98−1.90 (m, 1 H), 1.78 (ddq, J = 5.7, 7.4, 13.4 Hz, 1 H), 1.63 (ddq, J = 7.4, 8.4, 13.8 Hz, 1 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, MeOD-d_3) δ 174.6, 173.4, 173.3, 168.3, 138.2, 130.4, 129.4, 127.8, 56.5, 56.4, 55.8, 52.6, 38.8, 32.3, 31.1, 26.6, 26.5, 15.2, 10.7; mass spectrum (FAB) m/z 485.1895 ($C_{21}H_{32}N_4O_5S_2$ requires 485.1892), 460, 307, 289, 220, 205.

[1*R*,2*R*,3*S*,2(1′*R*,2′*S*)]-2-[2′-(Amino-L-cysteine)-1′-hydroxybutyl]-3-phenylcyclopropyl-1-carboxyl-L-methioninecarboxylic Acid Trifluoroacetate Salt (7). Prepared as an oil in 61% yield from **24** according to the procedure described for **6** [HPLC t_R 5 min (40% MeOH/59.9% H_2O/0.1% CF_3CO_2H)]: ^{1}H NMR (500 MHz, MeOD-d$_3$) δ 7.35−7.14 (comp, 5 H), 4.59 (dd, J = 4.6, 9.0 Hz, 1 H), 3.96 (dd, J = 5.1, 6.1 Hz, 1 H), 3.78 (dt, J = 4.2, 9.8 Hz, 1 H), 3.16 (dd, J = 3.8, 8.8 Hz, 1 H), 2.92 (dd, J = 5.1, 6.1 Hz, 2 H), 2.70 (dd, J = 5.1, 9.3 Hz, 1 H), 2.67−2.55 (m, 2 H), 2.50 (app t, J = 5.1 Hz, 1 H), 2.19−2.12 (m, 1 H), 2.10 (s, 3 H), 2.08−1.96 (m, 1 H), 1.87 (app t, J = 5.1, 9.3 Hz, 1 H), 1.43−1.30 (m, 2 H), 0.78 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, MeOD-d_3) δ 175.2, 174.9, 168.2, 137.6, 129.6, 129.5, 127.7, 58.3, 57.4, 55.9, 53.1, 53.0, 52.6, 32.4, 31.7, 31.2, 26.9, 25.6, 23.4, 15.2, 11.1; mass spectrum (FAB) m/z 484.1952 ($C_{22}H_{34}N_3O_5S_2$ requires 484.1940), 460, 443, 409, 391, 363, 329, 307.

[1*R*,2*S*,3*S*,2(1′*S*,2′*S*)]-2-[2′-(Amino-L-cysteine)-1′-hydroxybutyl]-3-phenylcyclopropane-1-carboxyl-L-methioninecarboxylic Acid Trifluoroacetate Salt (8). Prepared as an oil in 40% yield from **35a** according to the procedure described for **6**, *except* that acetonitrile was substituted for methanol for hydrolysis of the *N*,*S*-acetal and for purification of the product by reversed-phase chromatography [HPLC t_R 6 min (45% MeCN/54.9% H_2O/0.1% CF_3CO_2H)]: ^{1}H NMR (500 MHz, MeOD-d$_3$) δ 7.29−7.12 (comp, 5 H), 4.57 (dd, J = 4.7,

9.0 Hz, 1 H), 3.98 (dd, J = 4.9, 6.7 Hz, 1 H), 3.94−3.88 (comp, 2 H), 2.90 (dd, J = 4.9, 14.8 Hz, 1 H), 2.80 (dd, J = 6.7, 14.7 Hz, 1 H), 2.65−2.54 (comp, 3 H), 2.19 (dd, J = 5.1, 9.0 Hz, 1 H), 2.19−2.12 (m, 1 H), 2.09 (s, 3 H), 2.02−1.95 (m, 1 H), 1.76 (app t, J = 6.5, 9.0 Hz, 1 H), 1.69 (ddd, J = 5.1, 7.4, 13.8 Hz, 1 H), 1.51 (ddd, J = 7.4, 8.9, 13.8 Hz, 1 H), 0.93 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, MeOD-d_3) δ 175.3, 173.1, 168.2, 141.0, 129.6, 127.5, 127.4, 70.9, 57.9, 56.0, 53.1, 35.4, 32.4, 31.2, 30.1, 30.0, 26.7, 25.8, 23.8, 15.2, 10.9; mass spectrum (FAB) m/z 484.1937 ($C_{22}H_{34}N_3O_5S_2$ requires 484.1940), 466, 460, 381, 307, 289, 266.

[1*R*,2*S*,3*R*,2(1′*S*,2′*S*)]-2-[2′-(Amino-L-cysteine)-1′-hydroxybutyl]-3-phenylcyclopropane-1-carboxyl-L-methioninecarboxylic Acid Trifluoroacetate Salt (9). Prepared as a viscous oil in 11% yield from **35b** according to the procedure described for **6**, *except* that acetonitrile was substituted for methanol for hydrolysis of the *N*,*S*-acetal and for purification of the product by reversed-phase chromatography [HPLC t_R 6 min (45% MeCN/54.9% H_2O/0.1% CF_3CO_2H)]: ^{1}H NMR (500 MHz, MeOD-d$_3$) δ 7.36−7.15 (comp, 5 H), 4.59 (dd, J = 4.7, 9.2 Hz, 1 H), 4.08 (dd, J = 4.8, 6.7 Hz, 1 H), 3.98−3.95 (m, 1 H), 3.80 (dd, J = 2.2, 10.2 Hz, 1 H), 3.10 (dd, J = 4.8, 14.8 Hz, 1 H), 3.01 (dd, J = 6.7, 14.8 Hz, 1 H), 2.66 (dd, J = 9.4, 9.6 Hz, 1 H), 2.64−2.51 (m, 2 H), 2.23 (dd, J = 8.4, 9.4 Hz, 1 H), 2.21−2.12 (m, 1 H), 2.08 (s, 3 H), 2.03−1.97 (m, 1 H), 1.73 (ddd, J = 2.2, 8.4, 9.6 Hz, 1 H), 1.52−1.37 (m, 2 H), 0.69 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, MeOD-d_3) δ 175.0, 173.5, 168.5, 136.5, 131.1, 129.9, 129.1, 127.5, 68.9, 56.7, 56.1, 52.9, 32.1, 31.3, 29.1, 28.6, 26.7, 26.2, 25.1, 15.2, 10.9; mass spectrum (FAB) m/z 485.2031 ($C_{22}H_{34}N_3O_5S_2$ + H requires 485.2018), 466, 366, 278, 207.

(2*R*,4*S*,5*R*)-1-(L-Methionine)-5-[L-(*tert*-butyloxycarbonyl)dimethylthiazolidinecarboxamide]-4-[(*tert*-butyldimethysilyl)oxy-2-(phenylmethyl)heptanamide Trifluoroacetate Salt (10). Prepared from **43** in 57% yield as an oil using the procedure described for preparing **6**, *except* that acetonitrile was substituted for methanol for hydrolysis of the *N*,*S*-acetal and for purification of the product by reverse phase chromatography [HPLC t_R 10 min (30% MeCN/69.9% H_2O/0.1% CF_3CO_2H)]: ^{1}H NMR (500 MHz, MeOD-d_3) δ 7.27−7.15 (comp, 5 H), 4.45 (dd, J = 4.7, 9.4 Hz, 1 H), 3.93 (dd, J = 4.6, 7.4 Hz, 1 H), 3.68 (ddd, J = 2.9, 4.9, 9.2 Hz, 1 H), 3.54 (dt, J = 2.6, 10.6 Hz, 1 H), 2.98 (dd, J = 6.8, 13.0 Hz, 1 H), 2.94−2.87 (m, 2 H), 2.80 (dd, J = 7.5, 14.7 Hz, 1 H), 2.63 (dd, J = 7.8, 13.0 Hz, 1 H), 2.53−2.39 (m, 2 H), 2.14−2.07 (m, 1 H), 2.06 (s, 3 H), 1.98−1.92 (m, 1 H), 1.73−1.40 (comp, 5 H), 0.90 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, MeOD-d_3) δ 177.9, 174.9, 168.5, 140.6, 130.2, 129.5, 127.4, 70.9, 57.6, 56.2, 52.7, 46.2, 40.4, 36.8, 31.9, 31.3, 27.0, 25.0, 15.1, 11.1; mass spectrum (FAB) m/z (disulfide dimer) 969.3948 ($C_{44}H_{68}N_6O_{10}S_4$ + H requires 969.3958), 820, 671, 468. 434, 337, 285, 234, 216 (base).

Biological Assays. Compounds **6**−**10** were evaluated as inhibitors of purified recombinant human farnesyl transferase using an assay similar to a previously described protocol that had been modified to incorporate scintillation proximity assay (SPA) techniques with streptavidin-coated SPA beads.[38] Briefly, to an assay buffer containing the appropriate test compound, 25 nM biotinylated Tri-b Ala fragment (171−188) of Ki-Ras, and 55 nM tritiated farnesyl pyrophosphate was added purified recombinant human farnesyl transferase (final concentration 45 pg/well). The reaction was allowed to proceed for 30 min at room temperature and transferred to a streptavidin coated 96-well plate. The plate was washed, and the residual radioactivity was quantified. The IC_{50} determinations were determined using regression analysis by measuring inhibition of farnesylation from 8-point serial dilution of test compounds over a 1000-fold concentration range.

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Supporting Information Available: Copies of ^{1}H NMR spectra of all new compounds and 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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