Design, Synthesis, and Evaluation of Matrix Metalloprotease Inhibitors Bearing Cyclopropane-Derived Peptidomimetics as P1′ and P2′ Replacements

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We have previously used trisubstituted cyclopropanes as peptide replacements to induce conformational constraints in known pseudopeptide inhibitors of a number of important enzymes. Cyclopropane-derived peptide mimics are novel in that they are among the few replacements that locally orient the peptide backbone and the amino acid side chain in a predefined manner. Although these dipeptide isosteres have been employed to orient amino acid side chains mimicking the gauche(−) conformation of χ_1-space, their ability to project the side chains into an anti orientation has not been evaluated. As a first step toward this goal, the conformationally constrained pseudopeptides **8** and **10** and their corresponding flexible analogues **9** and **11** were prepared and tested as inhibitors of matrix metalloproteinases (MMPs). These compounds are analogues of **4** and **5**, which were known to be potent MMP inhibitors. The anti orientations of the isopropyl side chain in **8** and the aromatic ring in **10** relative to the peptide backbone substituents on the cyclopropane were predicted to correspond to the known orientations of the P1′ and P2′ side chains of **5** when bound to MMPs. Hence, **8** and **10** were designed explicitly to probe topological features of the S1′ or the S2′ binding pockets of the MMPs. They were also designed to explore the importance of the P1′−P2′ amide group, which is known to form highly conserved hydrogen bonds in several MMP-inhibitor complexes, and the viability of introducing a retro amide linkage between P2′ and P3′. Pseudopeptides **8** and **9** were found to be weak competitive inhibitors of a series of MMPs. Any entropically favorable conformational constraints that were induced by the cyclopropane in **8** were thus overwhelmed by the loss of the hydrogen bonding capability associated with the P1′−P2′ amide group. On the other hand, compounds **10** and **11,** which contain a P2′−P3′ retro amide group, were modest competitive inhibitors of a series of MMPs. The results obtained for **10** and **11** suggest that there may be a loss of hydrogen bonding capability associated with introducing the P2′−P3′ retro amide group. However, because the conformationally constrained pseudopeptide **10** was significantly more potent than its flexible analogue **11**, trisubstituted cyclopropanes related to **3** may serve as useful rigid dipeptide replacements in some biologically active pseudopeptides.

Introduction

The design of small rigid molecules that replicate the essential features of oligopeptide secondary structure is a central goal in efforts to identify peptide-like ligands having high affinity for biological targets. However, determining the conformation that a peptide adopts upon binding to its receptor, namely the biologically active conformation, is a major challenge. One general strategy that has been successfully used to gain insights regarding the structure of the bound peptide involves introducing conformational restraints into specific sites of the molecule and correlating the resultant biological activity with structure.[1] Most of the conformationally restricted replacements of peptide secondary structure reported to date are capable of controlling the organization of the backbone by imitating turns or helices, but there are only few mimics of an extended conformation,[2] which is important for pseudopeptide-like enzyme inhibitors. Controlling backbone conformation is not sufficient to optimize binding interactions because the amino acid side chains also contribute critical recognition elements for binding and specificity. Hence, a conformationally constrained dipeptide isostere capable of orienting the side chains while simultaneously constraining the backbone in an extended conformation would be a useful tool for drug discovery.

Toward addressing this critical need, we have developed novel replacements for a dipeptide array in which the backbone and the side chain of an amino acid residue are fixed in predetermined orientations by a cyclopropane ring.[3] The first type of these isosteres was obtained

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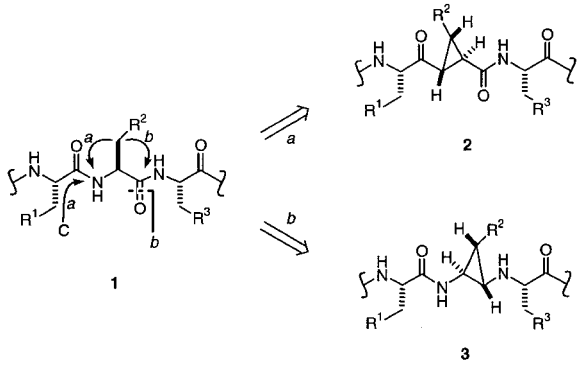
operationally by forming a bond between the β-carbon atom of an amino acid side chain in the peptide **1** to the *N*-terminal side of the α-carbon atom and replacing the amide nitrogen with a carbon atom (path a). The resulting pseudopeptides have the general structure **2**. The second type of replacement arises from forming a bond between the β-carbon and the carbonyl carbon atom on the *C*-terminal side of the α-carbon atom and replacing the carbonyl carbon atom with a tetrahedral carbon (path b). These conformationally constrained peptide mimics have the general structure **3**. When the backbone substituents on the cyclopropane ring are trans as shown in **2** and **3**, the backbone will be locally constrained in an extended conformation. Depending on the stereochemistry at the remaining cyclopropane carbon, the amino acid side chain can be positioned *relative to the backbone* in orientations that approximate χ_1-angles in **1** of gauche(−) (−60°), gauche(+) (+60°), or anti (±180°). Thus, the spatial position of the R^2 group in **2** corresponds closely to that found in the gauche(−) conformation, whereas that in **3** mimics an anti conformation.

Scheme 1



To evaluate 1,2,3-trisubstituted cyclopropane derivatives of **2** and **3** as peptide isosteres, we developed a number of efficient methods for the enantioselective syntheses of cyclopropanes bearing functionally diverse substituents.[4] Cyclopropanes, primarily those related to **2**, were then incorporated as rigid replacements into biologically active inhibitors of renin,[5] HIV-1 protease,[6] and Ras farnesyltransferase,[7] as well as enkephalin analogues[8] and SH2 antagonists.[9] Cyclopropanes have also been used by others as peptide mimics.[10] That cyclopropane-derived replacements actually stabilize or enforce the predicted structural properties was verified in a significant study in which truncated analogues of **2** were incorporated in conformationally restricted inhibitors of HIV-1 protease.[6] More recently, we have found that such replacements mimic bound conformations of the phosphotyrosine residue in high-affinity SH2 binding antagonists.[11]

Some years ago, we became interested in the possibility of introducing cyclopropane replacements into **4** and **5**, which were known to be nanomolar inhibitors of several matrix metalloproteases (MMPs).[12] The MMPs are a group of zinc-dependent enzymes that degrade the proteins of the extracellular matrix.[13] These enzymes are normally responsible for the turnover and destruction of tissues in processes such as growth, wound healing, and embryonic development. When the MMPs are not properly regulated, however, they are involved in a variety of pathological conditions including cancer,[14] arthritis,[15] and periodontal disease,[16] and inhibition of matrix metalloproteases has thus been of considerable interest in drug development. Numerous inhibitors of MMPs have been reported, and the best ones contain a functional group capable of chelating the zinc(II) ion in the active site, with the hydroxamic acid moiety providing the best potency;[17] however, few MMP inhibitors incorporate conformational constraints.[18]

In our first experiments directed toward evaluating conformationally constrained analogues of **4**, we prepared the cyclopropane-derived hydroxamates **6** and **7** in which the leucine side chain was simply joined to the peptide backbone by forming a carbon−carbon bond.[19] The cyclopropane ring at the P1′ subsite in each of these

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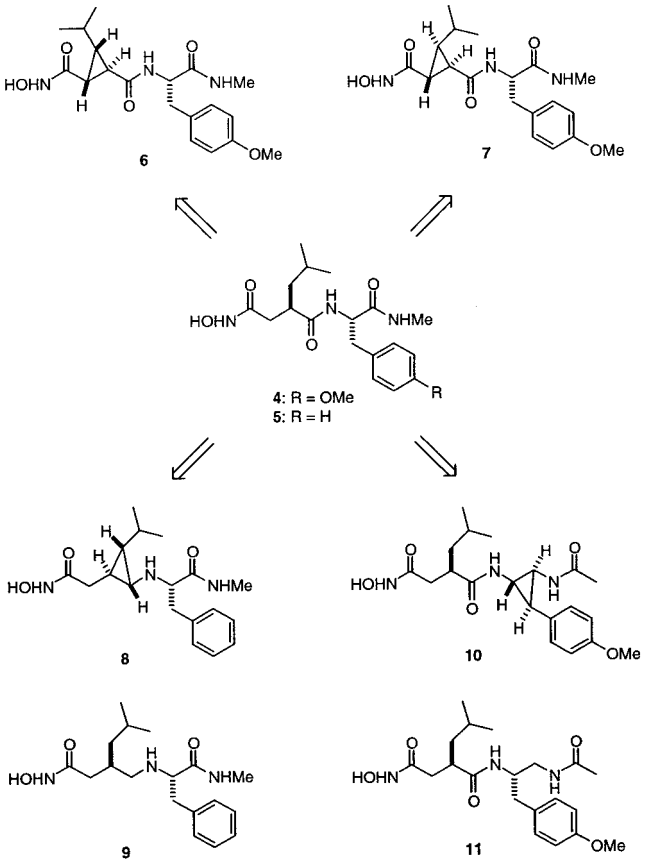
Scheme 2



pseudopeptides enforces a locally extended conformation on the backbone while orienting the isopropyl group in a gauche(−) orientation in **6** and a gauche(+) orientation in **7**. There were no structures of an MMP−inhibitor complex at the time **6** and **7** were prepared, so these ligands were designed to serve as preliminary probes of the biologically active conformation at the P1′ site of **4**. Because **6** and **7** exhibited only micromolar activities toward various MMPs, we concluded that the resident cyclopropanes in **6** and **7** were poor mimics of the bound conformation of **4**. We further speculated that the isopropyl group in **4** occupied an anti orientation in the bound conformation of **4** and related MMP inhibitors. This conjecture was subsequently verified by crystallographic and NMR studies of **5** bound to human fibroblast collagenase (MMP-1).[20,21]

The arena of MMP inhibitors thus offered an excellent opportunity to explore the properties of replacements generally related to **3** wherein the amino acid side chain would be projected in an anti conformation. The pseudopeptide **8** emerged as an attractive target because modeling suggested that the cyclopropane ring would nicely mimic the biologically active conformation at the P1′ subsite of **5** by positioning the isopropyl group in an anti orientation relative to the extended backbone of the inhibitor. It would then be necessary to prepare the corresponding flexible analogue **9** as a control so that the effects of introducing the conformational constraint could be reliably assessed. This is important because both **8** and **9** lack the P1′−P2′ amide linkage that was known to form highly conserved hydrogen bonds with Leu-181 and Pro-238 of the enzyme.[20] The pseudopeptides **8** and **9** would thus also probe the importance of these hydrogen bonds to binding affinity.

The X-ray crystallographic investigations of **5** bound to MMP-1 revealed that the aromatic ring of the P2′ residue was oriented in an anti conformation.[20] Even though these structural studies show that the P2′−P3′ amide functional group forms two hydrogen bonds with the Tyr-240 and Gly-179 residues of the enzyme, substitutions involving this amide linkage appear to be better tolerated in MMP inhibitors than those on the P1′−P2′ amide.[22] On the basis of these considerations, the cyclopropane containing pseudopeptide **10** emerged as a second intriguing target for evaluation. The *N*-acetyl group at the C-terminus of **10** forms a retro amide that maintains the amide character of this nitrogen, thereby allowing the formation of a hydrogen bond to Gly-179. Compound **11** would then serve as the appropriate control. The syntheses of the cyclopropane-containing peptide mimics **8** and **10** as well as their flexible analogues **9** and **11** and their inhibitory activities against several MMPs are described in this paper.

Results and Discussion

Synthesis of MMP Inhibitors with P1′ Replacements. The first step toward the synthesis of **8** entailed preparing the cyclopropyl lactone **13** (90% yield, 92% ee) by the enantioselective intramolecular cyclopropanation of the known allylic diazoacetate **12** using the chiral dirhodium catalyst Rh_2[5(*R*)-MEPY]$_4$.[4b,19] The absolute stereochemistry of the enantiomer of **13** had been previously established by the crystal X-ray structure of a protected tyrosine derivative.[4b] The lactone ring **13** was opened by reaction with *N*-methoxy-*N*-methylamine in the presence of Me_3Al according to the Weinreb protocol,[23] and the intermediate primary alcohol was oxidized with PCC to give **14** in 85% overall yield. Epimerization of the aldehyde group was achieved by heating **14** with an excess of triethylamine in methanol to give **15** in which the backbone substituents are trans.

The one-carbon homologation of the aldehyde group in **15** was achieved via a Peterson olefination using 2-lithio-2-trimethylsilyl-1,3-dithiane,[24] and hydrolysis of the hydroxamic acid group furnished **16** in 67% overall yield. Mercuric ion-promoted methanolysis of the ketene thioacetal moiety in **16** gave the desired methyl ester **17** in 73% yield.[25] It was necessary to monitor the progress of this reaction carefully, because prolonged reaction times led to formation of the dimethyl ester as a byproduct. The carboxylic acid group in **17** was transformed into a protected amino group in 53% yield by the stepwise

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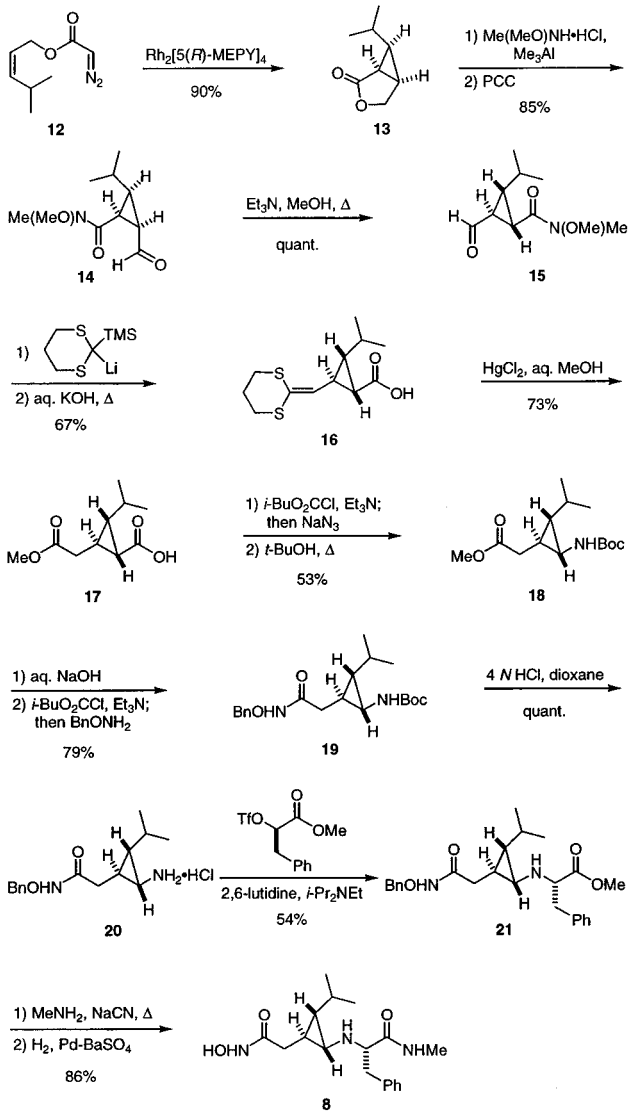
Scheme 3



Curtius procedure developed by Weinstock.[26] Preliminary experiments to effect the conversion of the methyl ester group in **18** to a protected hydroxamic acid group using *O*-benzylhydroxylamine in the presence of a variety of catalysts such as Me_3Al or NaCN were unsuccessful, even at elevated temperatures.[27] However, a two-step procedure involving saponification of the methyl ester followed by coupling of the derived mixed anhydride with *O*-benzylhydroxylamine gave the desired *O*-benzylhydroxamic acid **19** in 79% overall yield. The synthesis of the P1′ cyclopropylamine fragment **20** was completed by removing the Boc-protecting group from **19** by reaction with 4 N HCl in dioxane.

We had originally considered preparing a cyclopropane derivative of **4** by alkylating **20** with the triflate derived from D-3-(4-methoxyphenyl)lactate. However, it was not possible to convert *O*-methyl-D-tyrosine directly to methyl D-3-(4-methoxyphenyl)lactate using nitrous acid without partial racemization, so we decided to prepare the desmethoxy analogue **8** instead. Deletion of the aromatic methoxy group was not expected to have a significant effect upon the biological activity because the hydroxamates **4** and **5** have similar inhibitory activities toward several MMPs.[12] In the event, reaction of **20** with the triflate of D-phenyl lactate, which was prepared in situ from the corresponding hydroxy acid, gave the amine **21** in 54% yield.[8,28] The ester moiety of **21** was transformed into an *N*-methyl amide using methylamine in the presence of a catalytic amount of NaCN,[27b] and hydrogenolysis of the *O*-benzyl group using $Pd-BaSO_4$ as the catalyst gave **8** in 86% overall yield. The choice of the catalyst is crucial for this transformation, as it is known that Pd−C and other palladium catalysts may lead to extensive N−O bond cleavage.[29]

Remaining was the preparation of compound **9**, which is the flexible analogue of **8**, and our initial plan was to join the P1′ and P2′ subunits by a reductive amination of the aldehyde **24**. Thus, the known oxazolidinone imide **22**[30] was converted into the corresponding thioester **23**, which was reduced to aldehyde **24** with triethylsilane on Pd−C.[31] Although reductive amination of aldehydes with amino acid derivatives is well-known,[32] we found that the secondary amine formed from reaction of aldehyde **24** with H−Phe−NHMe was invariably contaminated with a diastereomer epimeric at the carbon bearing the isobutyl group. For example, reaction of the aldehyde **24** with H−Phe−NHMe in the presence of sodium triacetoxyborohydride gave an inseparable mixture (ca. 3:1) of the desired amine **27** and its epimer in 90% combined yield.[33]

All attempts to avoid epimerization during this reductive amination sequence were unsuccessful, so we turned our attention to preparing **27** by N-alkylation of H−Phe−NHMe. Toward this end, the oxazolidone imide **22** was converted to the corresponding alcohol **25** by reduction with lithium borohydride in the presence of MeOH.[34] Our initial plan was to react **25** with the dinitrobenzenesulfonamide of H−Phe−NHMe under Mitsunobu conditions to give a product in which the secondary amine functionality was already protected as an arylsulfonamide.[35] Unexpectedly, the 2,4-dinitrobenzenesulfonamide of H−Phe−NHMe was unstable under the coupling conditions, and the desired alkylation product was obtained in only 16% yield. Reaction of H−Phe−NHMe with a triflate, prepared in situ from alcohol **25**, did not give the desired amine **27** either. After considerable experimentation, we found that prolonged heating of the bromide **26**, which was prepared in 89% yield by treating **25** with CBr_4 and Ph_3P, with H−Phe−NHMe in the

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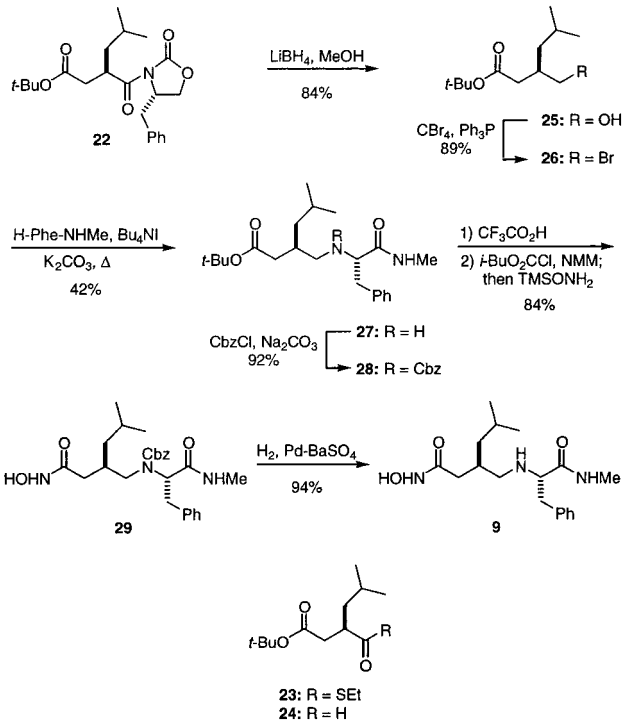
Scheme 4



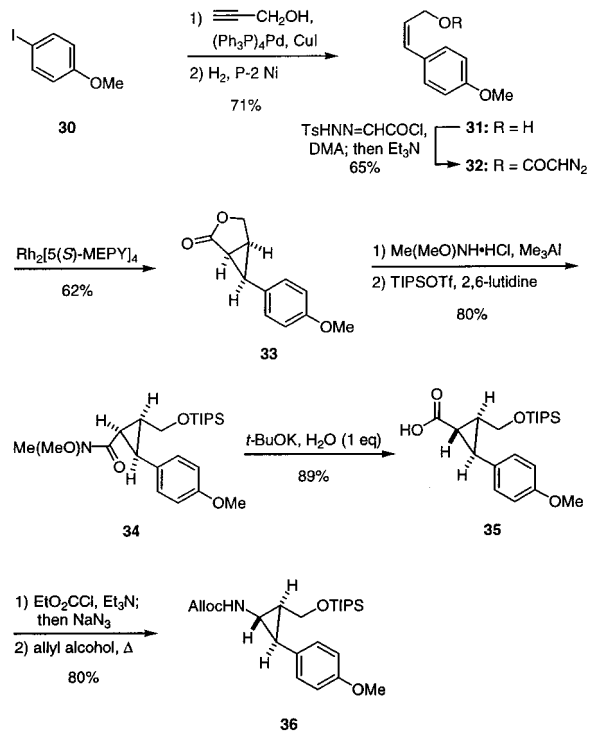
presence of potassium carbonate and catalytic amounts of tetrabutylammonium iodide gave the amine **27** in 42% yield.

Prior to converting the *tert*-butyl ester group in **27** to the requisite hydroxamic acid function, it was necessary to protect the secondary amine in order to prevent cyclization of an activated carboxylic acid to give a γ-lactam. Hence, **27** was converted to its carbamate **28** in 92% yield. Subsequent deprotection of the *tert*-butyl ester in **28** with trifluoroacetic acid gave the corresponding acid that was then activated with isobutyl chloroformate. Reaction of the mixed anhydride thus formed with *O*-(trimethylsilyl)hydroxylamine gave hydroxamic acid **29** in 84% overall yield from **28**. Deprotection of the amine functionality by hydrogenolysis employing Pd−$BaSO_4$ as the catalyst gave **9** in 94% yield. Although compound **9** tends to undergo lactamization at elevated temperatures, it is stable at room temperature in solution for several weeks.

Synthesis of MMP Inhibitors with P2′ Replacements. The opening move in the synthesis of the cyclopropane-derived pseudopeptide **10** involved the preparation of the requisite cyclopropyl lactone **33**, which would then be elaborated into **36**, the constrained P2′ subunit of **10**. *p*-Iodoanisole (**30**) was first coupled with propargyl alcohol via a Sonogashira reaction[36] to give an intermediate aryl propargyl alcohol that was reduced by catalytic hydrogenation over P-2 nickel to provide the allylic alcohol **31** in 71% overall yield. Transformation of **31** into the allylic diazoacetate **32** according to the standard Corey−Myers protocol[37] proceeded in 65% yield. It was necessary to use a slight excess of *N*,*N*-dimethylaniline (DMA) to avoid complications associated with acid-catalyzed isomerization of the double bond. When the diazoacetate **32** was heated in the presence of the chiral catalyst Rh_2[5(*S*)-MEPY]$_4$, the cyclopropyl lactone **33** was obtained in 62% yield (85% ee).[4a,b]

The lactone ring in **33** was then opened with *N*-methoxy-*N*-methylamine using the Weinreb protocol,[23] and the resulting primary alcohol was protected to give **34** in 80% overall yield. Hydrolysis of the hydroxamide moiety with anhydrous hydroxide in Et_2O proceeded with concomitant epimerization to give **35** in 89% yield.[38] The absolute stereochemistry at each of the cyclopropyl carbon atoms in **35** corresponded to that found in the pseudopeptide target **10**, and it remained to introduce the requisite nitrogen substituents via Curtius reactions. Although initial attempts to induce the Curtius reaction of **35** using diphenylphosphoryl azide were inefficient,[39] the stepwise procedure developed by Weinstock proved to be superior.[26] Thus, sequential reaction of **35** with ethyl chloroformate and NaN_3 afforded an intermediate acyl azide that underwent a Curtius rearrangement upon heating in the presence of allyl alcohol to give the allyloxycarbonyl (Alloc)-protected amine **36** in 80% yield.

Scheme 5



At this juncture, the synthetic plan called for appending the P1′ subunit by acylation of **36** with an activated derivative of the known carboxylic acid **37**.[30] Thus, **37** was first converted into the pentafluorophenyl ester **38** that was then coupled with the *N*-protected cyclopropane **36** in the presence of $(Ph_3P)_4Pd$ and Bu_3SnH using a one-pot deprotection−acylation sequence reported by Speckamp to give **39** in 84% yield.[40] Preliminary experiments directed toward converting the protected primary alcohol of **39** into a carboxylic acid that would be subjected to

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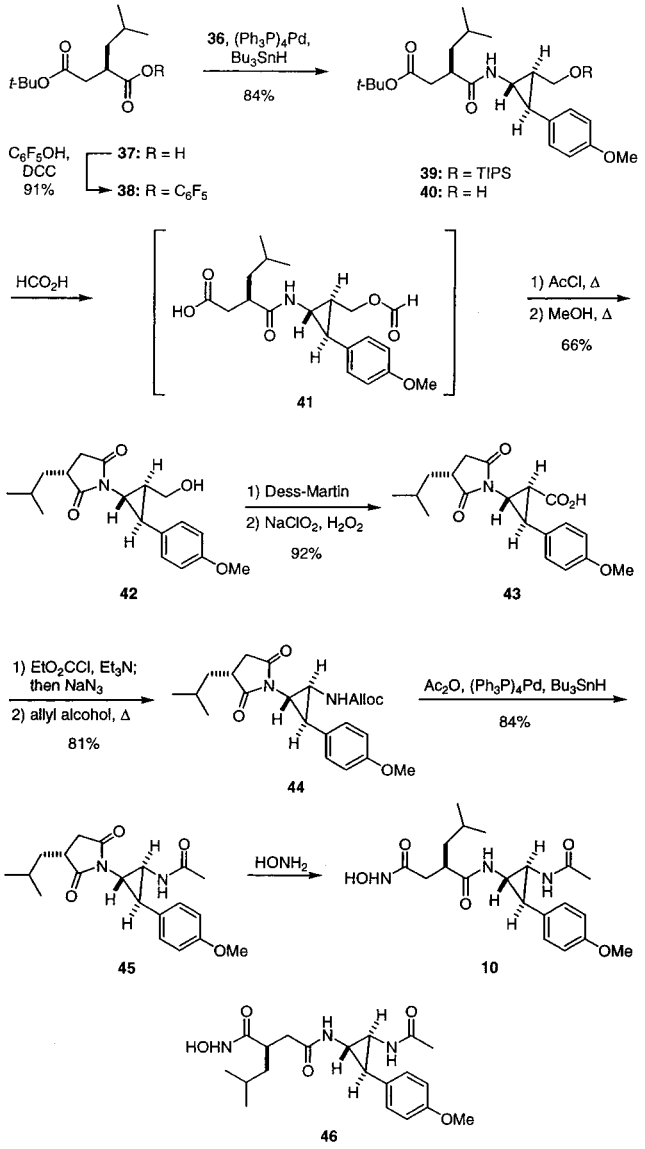
Scheme 6

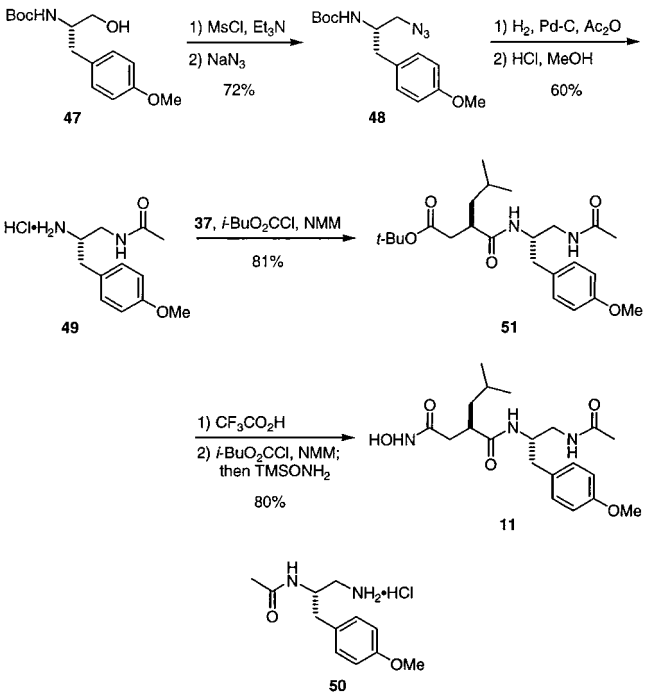


the second Curtius reaction were not encouraging. Namely, we were unable to cleanly oxidize the alcohol **40**. Although we did not rigorously identify the cause of the difficulty, we reasoned that the intermediate aldehyde was unstable as amino cyclopropanes bearing electron-withdrawing groups are known to suffer ring opening.[41]

To make the amide nitrogen in **39** less electron donating, we attempted to acylate it under a number of conditions but discovered that it was resistant to a bimolecular acylation. We were then attracted to the possibility that this nitrogen atom might undergo an intramolecular acylation to give a succinimide. Toward this end, **39** was treated with formic acid to give **41**, followed by cyclization to the succinimide in acetyl chloride. Subsequent removal of the formate ester in refluxing methanol provided the alcohol **42** in 66% overall yield from **39**. Although direct oxidation of the alcohol group in **42** to a carboxylic acid using a variety of oxidizing agents, including chromium and ruthenium reagents, proceeded in poor yields, a two-step procedure involving sequential oxidation with Dess−Martin periodinane and then sodium chlorite under buffered conditions furnished the acid **43** in 92% yield.[42] The transformation of **43** into the Alloc-protected amine **44** was achieved in 81% yield via the two-step Curtius procedure described previously. *N*-Acetylation of **44** according to the Speckamp protocol as before afforded **45** in 84% yield.

At this point, it was necessary to effect the regioselective opening of the succinimide ring in **45** to deliver the linear pseudopeptide **10**. The reaction of hydroxylamine with succinimides related to **45** had been reported to proceed with good to complete regioselectivity with attack on the less hindered carbonyl group.[43] We found, however, that reaction of **45** with recrystallized hydroxylamine hydrochloride under basic conditions provided a regioisomeric mixture (ca 2:1) of the hydroxamic acids **10** and **46**, respectively. Hence, the *N*-substituent in such imides plays an important role in directing the regiochemistry of imide cleavage. Although it was difficult to separate the major product **10** from **46**, pure **10** could be isolated by preparative thin-layer chromatography. The structure of **10** was assigned using a combination of COSY, NOESY, HMQC, and HMBC experiments on pure **10** and on a mixture of **10** and **46** that was enriched in **46**; we were unable to isolate **46** in pure form.

Scheme 7



Preparation of the hydroxamic acid **11**, which is the flexible analogue of **10**, was a far simpler task. *N*-Boc-*O*-methyl-L-tyrosinol[44] (**47**) was converted in two steps into the azide **48**. Reduction of the azide by catalytic hydrogenation in acetic anhydride, followed by removal of the *N*-Boc group with methanolic HCl, gave the monoprotected diamine **49** as its hydrochloride salt together with small amounts (<3%) of a compound that

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was tentatively identified as the transacylated amine hydrochloride **50**. Reaction of **49** with the mixed anhydride derived from **37** and isobutyl chloroformate furnished **51** in 81% yield. The carboxylic acid obtained upon treating **51** with trifluoroacetic acid was then converted into the desired hydroxamic acid **11** in 80% overall yield via sequential reaction with isobutyl chloroformate and *O*-(trimethylsilyl)hydroxylamine.

Biological Activities of 8−11. The cyclopropane-containing inhibitors **8** and **10**, their respective flexible analogues **9** and **11**, and the parent pseudopeptide **5** were tested for inhibitory activity against a number of MMPs using established assays.[45] Briefly, the matrilysin and stromelysin-1 assays were performed at pH 6.5, whereas the human fibroblast collagenase (HFC) and gelatinase A assays were performed at pH 7.4. Enzyme inhibition was measured using a flourimetric assay in which MMP-catalyzed cleavage of the peptide substrate Gly-Glu-(EDANS)-Gly-Pro-Leu-Gly-/-Leu-Tyr-Ala-Lys(DABCYL)-Gly (10 μM) was monitored using a concentration of enzyme that resulted in a 40-fold increase in fluorescence. The concentration of inhibitor ([Inh]) that resulted in 50% inhibition was determined by plotting the log[Inh] vs the log function of the % inhibition. The IC_{50} values were determined from a single assay using a regression analysis of the concentration/inhibition data with seven dilutions over a 1000-fold concentration range. The results of these bioassays are summarized in Table 1. For reference purposes, the hydroxamate **5**, which lacks the aryl methoxy group, is approximately equipotent with **4** against MMP-1.[12] Hence, an aryl methoxy group does not seem to have a significant impact on inhibitor potency, and **5** would thus appear to be a reasonable control for **10** and **11**.

Table 1. IC_{50} Values (μM) for MMP Inhibitors

compd	MMP-1 HFC	MMP-2 gelatinase A	MMP-3 stromelysin-1	MMP-7 matrilysin
5	0.0025	0.0007	0.016	0.0065
8	26% @100 μM	6.0	124	2.5% @100 μM
9	36% @ 10 μM	6.15	inactive @ 10 μM	40% @ 10 μM
10	0.054	0.064	1.0	0.78
11	1.9	0.26	6.9	6.7

Inspection of the results for the flexible pseudopeptide **9** clearly indicates that deleting the carbonyl carbon atom of the P1′−P2′ amide linkage in **5** had a dramatic and deleterious effect upon biological activity. Compound **9** was four orders of magnitude less potent an inhibitor of a series of MMPs than the parent hydroxamate **5**. Indeed, the IC_{50} values for HFC (MMP-1), stromelysin-1 (MMP-3), and matrilysin (MMP-7) were beyond the detection limit of the assay. The observation that **8** and **9** were approximately equipotent in these assays suggests that introducing a conformational constraint into **9** was insufficient to rescue activity. Inasmuch as the carbonyl oxygen atom and the amide N−H of the P1′−P2′ amide group form two highly conserved hydrogen bonds with the Leu-181 and Pro-238 residues of the MMP active site,[20] this loss of potency is perhaps not surprising. These interactions apparently do contribute significantly to the overall binding affinity. However, it is also important to recognize that the removal of the amide functional group also changes the hybridization and basicity of the nitrogen atom in the P1′−P2′ link. This nitrogen atom is approximately planar in the flexible inhibitor **5**, whereas it is tetrahedral in both **8** and **9**. The biological assays were typically conducted in the pH range of 6.5−7.4, so the nitrogen atoms in **8** and **9** should be protonated in bulk solvent. Hence, the ionic and polar character of **8** and **9** is very different from **5**.

Pseudopeptides **10** and **11** were considerably more potent than **8** and **9**, but they were still weaker inhibitors than the parent **5**. That the flexible analogue **11** was 400−1000 times less potent than **5** demonstrates that introduction of a retro amide replacement at the P2′−P3′ amide linkage is detrimental to activity. Modeling suggests that even though the NH group of **11** could be suitably positioned for forming a hydrogen bond with the carbonyl group of Gly-179 of the MMP, the *C*-terminal carbonyl group in **11** is probably displaced to the extent that it is no longer able to serve effectively as a hydrogen bond acceptor with the enzyme, especially to the Tyr-240 residue. What was particularly striking is that the conformationally constrained pseudopeptide **10** was significantly more potent (about 5−35-fold) than its flexible analogue **11**. Thus, despite the fact that introducing a retro amide moiety into the P2′−P3′ subsite of MMP inhibitors reduces potency, this loss can be at least partially restored by constraining the backbone and projecting the aromatic ring at the P2′ subsite in an approximately anti orientation.

Conclusions

The cyclopropane-derived pseudopeptides **8** and **10** and their flexible analogues **9** and **11** were prepared as derivatives of the corresponding MMP inhibitors **5** and **4**. These compounds were designed to test whether the introduction of a conformational constraint mimicking the biologically active conformation at the P1′ or P2′ subsites of **5** and **4** would enhance MMP binding affinity. Replacing the P1′−P2′ amide group of MMP inhibitors with a basic amino ethylene group is tremendously detrimental to enzyme binding. Indeed, the low biological activities of **8** and **9** do not allow any conclusions regarding whether substituted cyclopropanes of the general type **3** mimic the bound conformation of MMP inhibitors related to **5**. Although the introduction of a retro amide at P2′−P3′ of **4** was detrimental to potency, comparing the activities of **10** and **11** demonstrates for the first time that cyclopropane-containing pseudopeptides can have significantly higher activities than their flexible analogues. We previously found that rigidified pseudopeptides incorporating replacements derived from **2** were either equipotent or less active than their flexible derivatives.[5−8,11] The present results thus clearly signal that further investigations are necessary to understand the basis of these differences and to establish the scope and utility of cyclopropane-derived isosteres related to **3**.

Experimental Section

General. Unless otherwise noted, all solvents and reagents were reagent grade and used without purification. Tetrahydrofuran (THF) was distilled from potassium/benzophenone

(44) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051−6064.

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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. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Flash chromatography was performed using silica gel 60 (230−400 mesh ASTM) according to Still's protocol,[46] eluting with solvents as indicated. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in $CHCl_3$ 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 Me_4Si (TMS). Coupling constants are reported in hertz (Hz). The following are the designations for the spectral splitting patterns: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and app, apparent. Percent yields are given for compounds that were ≥95% pure as judged by NMR.

[1*S*-(1α,2α,3α)]-2-Hydroxymethyl-3-isopropylcyclopropane-1-carboxylic Acid *N*-Methoxy-*N*-methyl Amide. A solution of Me_3Al (2.0 M in hexane) (50 mL, 100 mmol) was added to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (8.35 g, 86 mmol) in CH_2Cl_2 (320 mL) at 0 °C. After the mixture was stirred for 25 min, a solution of **13**[4b,19] (2.00 g, 14 mmol) in CH_2Cl_2 (120 mL) was added at 0 °C, and stirring was continued at room temperature for 6 h. The reaction mixture was cooled to 0 °C, and 2 N aqueous HCl (75 mL) was slowly added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/hexane (2:1) to give 2.68 g (95%) of a colorless oil: ^1H NMR δ 4.05−3.95 (m, 2 H), 3.72 (s, 3 H), 3.18 (s, 3 H), 2.72 (br s, 1 H), 2.19−2.03 (m, 1 H), 1.93−1.84 (m, 1 H), 1.64 (app tt, J = 6.8, 8.9 Hz, 1 H), 1.21 (app dt, J = 8.9, 10.7 Hz, 1 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 173.7, 61.3, 58.4, 33.6, 32.6, 25.9, 22.9, 22.6, 19.0; IR ν 3501, 2962, 1636, 1463, 1384, 1097 cm^{-1}; MS *m*/*z* 202.1430 [$C_{10}H_{19}NO_3$ + H requires 202.1443], 184 (base), 154, 141.

[1*S*-(1α,2α,3α)]-2-Formyl-3-isopropylcyclopropane-1-carboxylic Acid *N*-Methoxy-*N*-methyl Amide (14). A mixture of pyridinium chlorochromate (6.03 g, 28 mmol) and Celite (4.00 g) was added to a solution of the alcohol from the preceding experiment (2.82 g, 14 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was suspended in Et_2O (150 mL) and filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with hexane/EtOAc (3:1) to give 2.48 g (89%) of **14** as a colorless oil: ^1H NMR δ 9.81 (d, J = 6.1 Hz, 1 H), 3.70 (s, 3 H), 3.16 (s, 3 H), 2.79−2.71 (m, 1 H), 2.43−2.32 (m, 1 H), 2.00−1.92 (m, 1 H), 1.54 (app dt, J = 8.9, 10.9 Hz, 1 H), 0.99 (app t, J = 7.1 Hz, 6 H); ^{13}C NMR δ 201.0, 170.5, 61.5, 36.3, 33.0, 32.6, 27.7, 22.7, 22.5, 22.4; IR ν 3018, 2965, 1693, 1649, 1462, 1392, 1094 cm^{-1}; MS *m*/*z* 200.1285 [$C_{10}H_{17}NO_3$ + H requires 200.1286] (base), 156, 139, 111.

[1*S*-(1α,2β,3α)]-2-Formyl-3-isopropylcyclopropane-1-carboxylic Acid *N*-Methoxy-*N*-methyl Amide (15). Neat Et_3N (23 mL, 165 mmol) was added to a solution of **14** (2.25 g, 11 mmol) in MeOH (570 mL), and the mixture was stirred at 70 °C for 72 h. The mixture was concentrated under reduced pressure to give 2.25 g (quantitative) of **15** as a colorless oil. Compound **15** could be used without purification: ^1H NMR δ 9.50 (d, J = 3.2 Hz, 1 H), 3.73 (s, 3 H), 3.18 (s, 3 H), 2.90−2.84 (m, 1 H), 2.57−2.54 (m, 1 H), 1.73−1.67 (m, 1 H), 1.65−1.60 (m, 1 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 199.4, 169.5, 61.6, 38.7, 35.0, 32.7, 26.8, 25.6, 22.4, 21.9; IR ν 3155, 2962, 1710, 1652, 1464, 1383, 1097 cm^{-1}; MS *m*/*z* 200.1283 [$C_{10}H_{17}NO_3$ + H requires 200.1286] (base), 182, 170, 142, 139, 111.

[1*S*-(1α,2β,3α)]-2-([1,3]-Dithiane-2-ylidenemethyl)-3-isopropylcyclopropane-1-carboxylic Acid *N*-Methoxy-*N*-methyl Amide. A solution of *n*-BuLi (1.52 M in hexane, 4.3 mL, 6.5 mmol) was added to a solution of 2-(trimethylsilyl)-1,3-dithiane (1.43 g, 7.4 mmol) in THF (40 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and cooled to −78 °C, and a solution of **15** (0.92 g, 4.7 mmol) in THF (25 mL) was added. The reaction mixture was stirred at −78 °C for 0.5 h, and then H_2O (40 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexane/EtOAc/CH_2Cl_2 (5:1:1) to yield 0.99 g (70%) of a colorless oil: (Note: the compound decomposes within hours in $CDCl_3$.) ^1H NMR δ 5.43 (d, J = 9.1 Hz, 1 H), 3.69 (s, 3 H), 3.16 (s, 3 H), 2.85−2.79 (comp, 4 H), 2.47 (ddd, J = 4.9, 6.1, 9.1 Hz, 1 H), 2.23−2.08 (comp, 3 H), 1.79−1.66 (m, 1 H), 1.05 (app dt, J = 6.1, 9.8 Hz, 1 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 171.7, 134.7, 125.7, 61.5, 38.5, 32.8, 30.3, 29.5, 26.6, 25.7, 25.6, 25.1, 22.5, 22.2; IR ν 3020, 2956, 1715, 1494, 1367, 1210, 1167 cm^{-1}; MS *m*/*z* 302.1243 [$C_{14}H_{23}NO_2S_2$ + H requires 302.1248], 272, 241 (base), 135.

[1*S*-(1α,2β,3α)]-2-([1,3]-Dithiane-2-ylidenemethyl)-3-isopropylcyclopropane-1-carboxylic Acid (16). A solution of 10% aqueous KOH (20 mL) was added to a solution of the *N*-methoxy-*N*-methyl amide from the preceding experiment (721 mg, 2.4 mmol) in EtOH (20 mL), and the mixture was heated under reflux for 26 h. The EtOH was removed under reduced pressure, and the resulting aqueous solution was washed with Et_2O (8 mL). The aqueous layer was acidified to pH = 4 by adding 4 N aqueous HCl and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 595 mg (96%) of **16** as a white foam that was used without further purification: (Note: the compound decomposes within hours in $CDCl_3$.) ^1H NMR δ 5.36 (d, J = 9.1 Hz, 1 H), 2.90−2.82 (comp, 4 H), 2.42 (ddd, J = 4.8, 6.6, 9.1 Hz, 1 H), 2.18−2.11 (comp, 2 H), 1.83−1.76 (m, 1 H), 1.74 (dd, J = 4.8, 9.4 Hz, 1 H), 1.11 (app dt, J = 6.6, 9.4 Hz, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 178.4, 132.7, 127.1, 39.1, 30.1, 29.4, 28.8, 27.5, 26.1, 24.9, 22.4, 22.0; IR ν 3018, 2964, 1695, 1522, 1424, 1216 cm^{-1}; MS *m*/*z* 259.0820 [$C_{12}H_{18}O_2S_2$ + H requires 259.0826] (base), 241, 213, 135, 107.

[1*R*-(1α,2α,3β)]-2-Isopropyl-3-methoxylcarbonylmethylcyclopropane-1-carboxylic Acid (17). Mercury(II) chloride (1.50 g, 5.5 mmol) was added to a solution of **16** (0.65 g, 2.5 mmol) in MeOH/H_2O (9:1, 120 mL), and the mixture was heated at 70 °C for 2 h. The mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with hexane/EtOAc/AcOH (75:25:1) to give 0.37 g (73%) of **17** as a white solid: mp 70−72 °C; ^1H NMR δ 3.66 (s, 3 H), 2.45 (dd, J = 6.4, 15.9 Hz, 1 H), 2.15 (dd, J = 8.0, 15.9 Hz, 1 H), 1.74−1.63 (comp, 2 H), 1.55 (dd, J = 4.8, 9.1 Hz, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.00−0.93 (m, 1 H), 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 178.6, 172.2, 51.7, 38.2, 37.7, 26.3, 25.0, 23.6, 22.2, 22.1; IR ν 3515, 2960, 1733, 1697, 1456, 1177 cm^{-1}; MS *m*/*z* 200.1036 [$C_{10}H_{16}O_4$ requires 200.1049], 183 (base), 169, 155, 141, 127, 109.

[1*R*-(1α,2α,3β)]-2-Isopropyl-3-methoxylcarbonylmethylcyclopropane-1-carbamic Acid *tert*-Butyl Ester (18). Isobutyl chloroformate (263 μL, 2.0 mmol) was added to a solution of **17** (290 mg, 1.5 mmol) and Et_3N (263 μL, 1.9 mmol) in acetone/H_2O (10:1, 5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 0.5 h, and a solution of sodium azide (151 mg, 2.3 mmol) in H_2O (0.4 mL) was added. The reaction mixture was stirred at −10 °C for 1 h and then partitioned between CH_2Cl_2 (8 mL) and H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was dissolved in *t*-BuOH (8 mL);

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

the reaction mixture was heated under reflux for 16 h, and the solvent was removed under reduced pressure. The yellow solid was purified by flash chromatography eluting with hexane/EtOAc (5:1) to give 215 mg (53%) of **18** as a white solid: mp 83−87 °C; ^{1}H NMR δ 4.64 (br s, 1 H), 3.66 (s, 3 H), 2.57 (dd, J = 6.1, 15.8 Hz, 1 H), 2.36−2.50 (m, 1 H), 2.03 (dd, J = 8.2, 15.8 Hz, 1 H), 1.43 (s, 9 H), 1.25−1.19 (m, 1 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.88−0.78 (m, 1 H), 0.59−0.49 (m, 1 H); ^{13}C NMR δ 172.9, 156.6, 79.4, 51.5, 37.2, 34.0, 32.6, 28.3, 27.5, 22.4, 21.0; IR ν 3020, 2956, 1715, 1494, 1367, 1210, 1167 cm^{-1}; MS m/z 272.1860 [$C_{14}H_{25}NO_4$ + H requires 272.1862], 256, 244, 216 (base), 172.

[1*R*-(1α,2α,3*β*)]-3-Carboxymethyl-2-isopropylcyclopropane-1-carbamic Acid *tert*-Butyl Ester. A solution of 1 N aqueous NaOH (1.1 mL, 1.1 mmol) was added to a solution of **18** (202 mg, 0.75 mmol) in EtOH (6 mL), and the mixture was heated at 75 °C for 1 h. The solution was concentrated under reduced pressure, and the resulting semisolid was dissolved in H_2O (3 mL) and EtOAc (6 mL). The aqueous layer was acidified to pH = 4 by adding 1.5 N aqueous HCl, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 6 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 185 mg (96%) of a white solid, mp 132−134 °C, which was used in the next step without further purification: ^{1}H NMR (CD_3OD) δ 2.48−2.40 (comp, 2 H), 2.10 (dd, J = 8.0, 15.9 Hz, 1 H), 1.44 (s, 9 H), 1.27−1.13 (m, 1 H), 1.03 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 0.91−0.82 (m, 1 H), 0.49 (ddd, J = 6.0, 7.1, 10.0 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 176.4, 159.4, 80.2, 38.3, 35.2, 34.1, 28.7, 28.4, 22.9, 22.8, 20.6; IR ν 3019, 2977, 1716, 1694, 1505, 1216 cm^{-1}; MS m/z 258.1705 [$C_{13}H_{23}NO_4$ + H requires 258.1705], 242, 230, 202 (base), 184, 158.

[1*R*-(1α,2α,3*β*)]-3-Benzoxycarbamoylmethyl-2-isopropylcyclopropane-1-carbamic Acid *tert*-Butyl Ester (19). Isobutyl chloroformate (111 μL, 0.85 mmol) was added dropwise to a solution of the acid from the preceding reaction (183 mg, 0.71 mmol) and Et_3N (139 μL, 0.99 mmol) in THF (4 mL) at −10 °C. The mixture was stirred for 20 min, whereupon *O*-benzylhydroxylamine (175 μL, 1.4 mmol) was added dropwise at −10 °C. The mixture was stirred at room temperature for 12 h; the solvent was partially removed under reduced pressure, and EtOAc (5 mL) was added. The organic layer was washed with 0.5 N aqueous HCl (1 × 3 mL), and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography eluting with hexane/EtOAc (1:1) to yield 211 mg (82%) of **19** as a white solid: mp 119−123 °C; ^{1}H NMR δ 12.05 (br s, 1 H), 7.44−7.26 (comp, 5 H), 4.99 (d, J = 11.4 Hz, 1 H), 4.96 (d, J = 11.4 Hz, 1 H), 4.76 (br s, 1 H), 2.78 (dd, J = 2.7, 17.7 Hz, 1 H), 2.24 (dd, J = 2.9, 7.5 Hz, 1 H), 1.65 (dd, J = 11.3, 17.7 Hz, 1 H), 1.43 (s, 9 H), 1.29−1.21 (m, 1 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.77−0.72 (m, 1 H), 0.40 (ddd, J = 5.8, 7.5, 10.2 Hz, 1 H); ^{13}C NMR δ 168.1, 158.2, 136.2, 128.9, 128.2, 128.1, 80.8, 77.5, 38.5, 33.8, 32.2, 28.3, 27.1, 22.6, 22.3, 20.5; IR ν 3442, 3172, 2993, 1701, 1666, 1498, 1161 cm^{-1}; MS m/z 363.2278 [$C_{20}H_{30}N_2O_4$ + H requires 363.2284], 335, 307 (base), 257, 217, 201, 156, 140.

[1*R*-(1α,2α,3*β*)]-3-Benzoxycarbamoylmethyl-2-isopropylcyclopropylamine Hydrochloride (20). A solution of **19** (85 mg, 0.23 mmol) in 4 N HCl in dioxane (1 mL) was stirred at room temperature for 10 min, and the solvent was removed under reduced pressure. The resulting white foam was triturated with Et_2O (2 × 2 mL) to afford 69 mg (quantitative) of **20** as a white solid, mp 65 °C (dec). This material was used in the next step without further purification: ^{1}H NMR (CD_3OD) δ 7.43−7.33 (comp, 5 H), 4.85 (s, 2 H), 2.53 (dd, J = 3.7, 7.8 Hz, 1 H), 2.19 (dd, J = 6.8, 15.0 Hz, 1 H), 2.03 (dd, J = 7.2, 15.0 Hz, 1 H), 1.40−1.26 (m, 1 H), 1.17−1.08 (m, 1 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.81−0.73 (m, 1 H); ^{13}C NMR (CD_3OD) δ 170.6, 136.9, 130.2, 129.7, 129.5, 79.1, 35.4, 33.8, 31.4, 28.0, 22.9, 22.6, 20.5; IR (CH_2Cl_2) ν 3054, 2986, 1662, 1422, 1264 cm^{-1}; MS m/z 263.1771 [$C_{15}H_{22}N_2O_2$ + H requires 263.1760] (base), 246, 157, 140, 107.

***N*-{[1*R*-(1α,2α,3*β*)]-3-Benzoxycarbamoylmethyl-2-isopropylcyclopropyl}-L-phenylalanine Methyl Ester (21).** Freshly distilled trifluoromethanesulfonic anhydride (57 μL, 0.35 mmol) was slowly added to a solution of methyl D-3-phenyllactate (63 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, and 2,6-lutidine (41 μL, 0.35 mmol) was added. Stirring at 0 °C was continued for an additional 15 min, whereupon *i*-Pr_2NEt (72 μL, 0.41 mmol) was added. A mixture of **20** (35 mg, 0.12 mmol) and *i*-Pr_2NEt (31 μL, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred at room temperature for 12 h. A portion of CH_2Cl_2 (3 mL) was added, and the solution was washed with brine (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography eluting with hexane/EtOAc (2:1) to yield 28 mg (54%) of **21** as a colorless oil: ^{1}H NMR (CD_3OD) δ 7.41−7.31 (comp, 5 H), 7.24−7.13 (comp, 5 H), 4.82 (s, 2 H), 3.63 (s, 3 H), 3.56 (app t, J = 6.9 Hz, 1 H), 2.90 (dd, J = 6.4, 13.4 Hz, 1 H), 2.82 (dd, J = 7.4, 13.4 Hz, 1 H), 2.02 (dd, J = 3.2, 7.5 Hz, 1 H), 1.91 (dd, J = 6.8, 14.3 Hz, 1 H), 1.81 (dd, J = 7.8, 14.3 Hz), 1.42−1.34 (m, 1 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.53−0.48 (m, 1 H), 0.35 (ddd, J = 5.6, 7.5, 10.0 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 176.9, 172.0, 139.1, 137.0, 130.4, 130.1, 129.6, 129.5, 129.2, 127.5, 79.1, 64.2, 52.1, 41.2, 40.6, 37.0, 35.8, 27.9, 23.1, 22.9; IR ν 3401, 2955, 1731, 1689, 1456, 1174 cm^{-1}; MS m/z 425.2444 [$C_{25}H_{32}N_2O_4$ + H requires 425.2440] (base), 319, 301, 274.

***N*-{[1*R*-(1α,2α,3*β*)]-3-Benzoxycarbamoylmethyl-2-isopropylcyclopropyl}-L-phenylalanine *N*′-Methyl Amide.** A solution of **21** (25 mg, 0.059 mmol) in 33% ethanolic $MeNH_2$ (2 mL) containing NaCN (0.5 mg, 0.010 mmol) was heated in a closed vial at 55 °C for 17 h. The solvent was removed under reduced pressure, and the resulting crude product was purified by flash chromatography eluting with $CHCl_3$/MeOH (100:1) to give 23 mg (90%) of a white solid: mp 126−130 °C; ^{1}H NMR (CD_3OD) δ 7.42−7.33 (comp, 5 H), 7.26−7.14 (comp, 5 H), 4.84 (d, J = 10.9 Hz, 1 H), 4.80 (d, J = 10.9 Hz, 1 H), 3.34−3.29 (m, 1 H), 2.86 (dd, J = 7.1, 13.4 Hz, 1 H), 2.74 (dd, J = 7.4, 13.4 Hz, 1 H), 2.63 (s, 3 H), 2.00−1.86 (comp, 2 H), 1.80 (dd, J = 7.9, 14.4 Hz, 1 H), 1.38−1.21 (m, 1 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.52−0.43 (m, 1 H), 0.34 (ddd, J = 5.6, 7.5, 10.0 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 177.4, 172.2, 139.4, 136.9, 130.4, 130.3, 129.7, 129.5, 129.3, 127.5, 79.1, 65.4, 41.2, 40.6, 36.8, 35.6, 28.0, 26.0, 23.1, 22.8; IR ν 3226, 2957, 1652, 1461, 1406, 1124 cm^{-1}; MS m/z 424.2590 [$C_{25}H_{33}N_3O_3$ + H requires 424.2600], 333, 318, 273, 259, 179 (base), 164, 140, 120.

***N*-{[1*R*-(1α,2α,3*β*)]-3-Hydroxycarbamoylmethyl-2-isopropylcyclopropyl}-L-phenylalanine *N*′-Methyl Amide (8).** A solution of the *O*-benzyl hydroxamate from the preceding experiment (16 mg, 0.038 mmol) in MeOH (1 mL) containing 5% Pd−$BaSO_4$ (16 mg) was shaken under a H_2 atmosphere (40 psi) for 15 h. The catalyst was removed by vacuum filtration through a Celite pad, which was then washed with MeOH (4 mL). The combined filtrates were concentrated under reduced pressure, and the resulting yellow oil was triturated with hexane (2 × 1 mL) to afford 12 mg (95%) of **8** as a pale yellow solid: mp 48 °C dec; ^{1}H NMR (CD_3OD) δ 7.27−7.15 (comp, 5 H), 3.33−3.28 (m, 1 H), 2.85 (dd, J = 7.5, 13.4 Hz, 1 H), 2.75 (dd, J = 7.5, 13.4 Hz, 1 H), 2.67 (s, 3 H), 2.02 (dd, J = 6.3, 14.5 Hz, 1 H), 1.93 (dd, J = 3.2, 7.5 Hz, 1 H), 1.76 (dd, J = 8.3, 14.5 Hz, 1 H), 1.37−1.29 (m, 1 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.54−0.45 (m, 1 H), 0.36 (ddd, J = 5.6, 7.5, 9.9 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 177.6, 172.3, 139.4, 130.3, 129.3, 127.5, 65.5, 41.3, 40.6, 36.9, 35.7, 28.0, 26.0, 23.1, 23.0; IR ν 3358, 3230, 2958, 1658, 1540, 1464, 1087 cm^{-1}; MS m/z 334.2130 [$C_{18}H_{27}N_3O_3$ + H requires 334.2131], 318, 301, 273 (base), 259, 179, 120.

(3*R*)-3-Hydroxymethyl-5-methylhexanoic Acid *tert*-Butyl Ester (25). A solution of **22**[30] (4.59 g, 11.8 mmol) and $LiBH_4$ (257 mg, 11.8 mmol) in Et_2O (60 mL) containing MeOH (478 μL, 11.8 mmol) was stirred at 0 °C for 1.5 h. Saturated

aqueous Na_2CO_3 (60 mL) was added, and the biphasic mixture was stirred at room temperature for 0.5 h to ensure complete hydrolysis of the boranes. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with pentane/Et_2O (1:1) to yield 2.15 g (84%) of **25** as a colorless liquid: ^{1}H NMR δ 3.63 (dd, J = 11.0, 4.4 Hz, 1 H), 3.46 (dd, J = 11.0, 7.0 Hz, 1 H), 2.29 (dd, J = 15.1, 7.4 Hz, 1 H), 2.24 (dd, J = 15.1, 5.4 Hz, 1 H), 2.08−2.00 (m, 1 H), 1.67−1.59 (m, 1 H), 1.44 (s, 9 H), 1.23−1.17 (m, 1 H), 1.13−1.07 (m, 1 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 173.3, 80.6, 66.0, 40.4, 38.4, 35.7, 28.1, 25.2, 22.8, 22.6; IR ν 3442, 1713, 1369, 1155 cm^{-1}; MS m/z 217.1804 [$C_{12}H_{24}O_5$ + H requires 217.1804], 161 (base), 143.

(3*R*)-3-Bromomethyl-5-methylhexanoic Acid *tert*-Butyl Ester (26). Solid Ph_3P (3.80 g, 14.5 mmol) was added to a mixture of **25** (2.09 g, 9.66 mmol) and CBr_4 (4.81 g, 14.5 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 2 h, and the solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography eluting with pentane/Et_2O (20:1) to yield 2.41 g (89%) of **26** as a colorless liquid: ^{1}H NMR δ 3.53 (dd, J = 10.0, 3.8 Hz, 1 H), 3.44 (dd, J = 10.0, 5.4 Hz, 1 H), 2.37 (dd, J = 15.3, 6.8 Hz, 1 H), 2.24−2.15 (comp, 2 H), 1.65−1.56 (m, 1 H), 1.43 (s, 9 H), 1.35−1.27 (m, 1 H), 1.18−1.13 (m, 1 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 171.7, 80.5, 41.8, 39.0, 39.0, 34.3, 28.1, 25.0, 22.9, 22.3; IR ν 1717, 1368, 1257, 1156 cm^{-1}; MS m/z 279.0954 [$C_{12}H_{23}BrO_2$ + H requires 279.0960], 255, 223 (base), 143.

(3*R*)-5-Methyl-3-[(1*S*)-(1-methylcarbamoyl-2-phenylethylamino)methyl]hexanoic Acid *tert*-Butyl Ester (27). A mixture of **26** (1.26 g, 4.50 mmol), phenylalanine *N*-methyl amide (1.60 g, 9.00 mmol), solid K_2CO_3 (1.24 g, 9.00 mmol), and Bu_4NI (166 mg, 0.450 mmol) in DMF (23 mL) was stirred at 60 °C for 6 days. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (20 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the resulting yellow oil was purified by flash chromatography eluting with hexane/EtOAc (1:1) to yield 705 mg (42%) of **27** as a yellow oil: ^{1}H NMR δ 7.34−7.18 (comp, 6 H), 3.27−3.20 (comp, 2 H), 2.81 (d, J = 5.0 Hz, 3 H), 2.63 (app t, J = 11.3 Hz, 1 H), 2.40 (dd, J = 11.8, 4.6 Hz, 1 H), 2.31 (dd, J = 11.8, 5.0 Hz, 1 H), 2.15−2.07 (m, 2 H), 1.90−1.87 (m, 1 H), 1.39 (s, 9 H), 1.30−1.22 (comp, 2 H), 0.94−0.85 (m, 2 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.69 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 174.2, 172.6, 137.8, 129.0, 128.8, 126.9, 80.3, 64.3, 51.4, 41.2, 39.3, 39.2, 33.2, 28.1, 25.8, 24.9, 22.8, 22.4; IR ν 3443, 3375, 2400, 1716, 1662, 1526, 1475, 1423, 1223, 728, 670 cm^{-1}; MS m/z 377.2809 [$C_{22}H_{36}N_2O_5$ + H requires 377.2804] (base), 318.

(3*R*)-3-{[Benzyloxycarbonyl-(1*S*)-(1-methylcarbamoyl-2-phenylethyl)amino]methyl}-5-methylhexanoic Acid *tert*-Butyl Ester (28). A solution of **27** (598 mg, 1.59 mmol) in THF/H_2O (3:1, 13 mL) was adjusted to pH = 10 by adding saturated aqueous Na_2CO_3. Benzyl chloroformate (453 μL, 3.18 mmol) was added, and the solution was stirred at room temperature for 0.5 h while maintaining a pH of 10 by adding saturated aqueous Na_2CO_3. The THF was evaporated under reduced pressure. A solution of 10% aqueous citric acid was added to adjust the pH to 4, and the mixture was then extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexane/EtOAc (2:1) to yield 743 mg (92%) of **28** as a yellow oil: ^{1}H NMR (DMSO-d_6, 90 °C) δ 7.48−7.43 (m, 1 H), 7.37−7.29 (comp, 5 H), 7.23−7.14 (comp, 5 H), 5.08 (d, J = 12.5 Hz, 1 H), 5.04 (d, J = 12.5 Hz, 1 H), 4.44 (app t, J = 7.5 Hz, 1 H), 3.24 (dd, J = 13.8, 7.0 Hz, 1 H), 3.13 (dd, J = 14.3, 8.3 Hz, 1 H), 3.05−2.97 (comp, 2 H), 2.58 (d, J = 4.6 Hz, 3 H), 2.17−2.10 (comp, 2 H), 1.87 (dd, J = 14.3, 6.9 Hz, 1 H), 1.53−1.47 (m, 1 H), 1.38 (s, 9 H), 1.07−0.96 (m, 2 H), 0.79 (d, J = 6.6 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 90 °C) δ 171.1, 169.2, 155.6, 137.8, 136.2, 128.4, 127.7, 127.6, 127.2, 127.2, 125.7, 78.9, 66.1, 61.7, 50.1, 41.1, 37.6, 35.1, 32.1, 27.3, 25.2, 24.2, 22.2, 22.0; IR ν 3442, 3350, 1708, 1682, 1368, 1235, 1154 cm^{-1}; MS m/z 511.3170 [$C_{30}H_{42}N_2O_5$+H requires 511.3172], 455 (base), 377.

(3*R*)-3-{[Benzyloxycarbonyl-(1*S*)-(1-methylcarbamoyl-2-phenylethyl)amino]methyl}-5-methylhexanoic Acid. A solution of **28** (670 mg, 1.31 mmol) in a mixture of CF_3CO_2H (13 mL) and CH_2Cl_2 (13 mL) was stirred at room temperature for 0.5 h. Toluene (10 mL) was added, and the solution was concentrated under reduced pressure. The residual CF_3CO_2H was removed by azeotropic distillation under reduced pressure with toluene (2 × 10 mL). The resulting yellow oil was purified by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) to yield 591 mg (99%) of a white foam: ^{1}H NMR (DMSO-d_6, 90 °C) δ 11.53 (br s, 1 H), 7.47−7.42 (m, 1 H), 7.37−7.29 (comp, 5 H), 7.23−7.14 (comp, 5 H), 5.09 (d, J = 12.6 Hz, 1 H), 5.04 (d, J = 12.6 Hz, 1 H), 4.43 (app t, J = 7.5 Hz, 1 H), 3.24 (dd, J = 13.8, 6.9 Hz, 1 H), 3.16 (dd, J = 14.2, 6.4 Hz, 1 H), 3.02−2.96 (comp, 2 H), 2.58 (d, J = 4.6 Hz, 3 H), 2.20 (dd, J = 15.1, 5.1 Hz, 1 H), 2.18−2.13 (m, 1 H), 1.95 (dd, J = 15.1, 7.2 Hz, 1 H), 1.53−1.48 (m, 1 H), 1.08−0.99 (m, 2 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 90 °C) δ 173.2, 169.3, 155.6, 137.8, 136.3, 128.4, 127.7, 127.6, 127.2, 127.2, 125.6, 66.1, 61.7, 50.2, 41.2, 36.4, 35.0, 31.9, 25.2, 24.2, 22.2, 22.0; IR ν 3448, 2400, 1683, 1523, 1423, 1475, 1210, 768, 671 cm^{-1}; MS m/z 455.2528 [$C_{26}H_{34}N_2O_5$ + H requires 455.2546] (base), 411, 321, 303, 244.

(2*R*)-(2-Hydroxycarbamoylmethyl-4-methylpentyl)-(1*S*)-(1-methylcarbamoyl-2-phenylethyl)carbamic Acid Benzyl Ester (29). Isobutyl chloroformate (197 μL, 1.52 mmol) was added to a solution of the acid from the preceding reaction (575 mg, 1.26 mmol) and *N*-methylmorpholine (195 μL, 1.77 mmol) in THF (6.5 mL) at −10 °C. The mixture was stirred at −10 °C for 0.5 h, and *O*-(trimethylsilyl)hydroxylamine (201 μL, 1.64 mmol) was added. The cooling bath was removed, and the mixture was stirred for 4 h at room temperature. The THF was removed under reduced pressure, and the resulting yellow oil was purified by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) to yield 501 mg (85%) of **29** as a white solid: mp 75−77 °C; ^{1}H NMR (DMSO-d_6, 90 °C) δ 10.00 (br s, 1 H), 8.31 (br d, J = 14.4 Hz, 1 H), 7.48−7.43 (m, J = 4.6 Hz, 1 H), 7.37−7.29 (comp, 5 H), 7.23−7.14 (comp, 5 H), 5.10 (d, J = 12.6 Hz, 1 H), 5.04 (d, J = 12.6 Hz, 1 H), 4.36 (app t, J = 7.5 Hz, 1 H), 3.26 (dd, J = 13.8, 6.8 Hz, 1 H), 3.16 (dd, J = 14.3, 8.5 Hz, 1 H), 3.00 (dd, J = 13.8, 8.2 Hz, 1 H), 2.87 (dd, J = 14.3, 5.7 Hz, 1 H), 2.59 (d, J = 4.6 Hz, 3 H), 2.15−2.08 (m, 1 H), 2.02 (br d, J = 14.1 Hz, 1 H), 1.75−1.87 (m, 1 H), 1.52−1.44 (m, 1 H), 1.07−1.02 (m, 1 H), 0.97−0.92 (m, 1 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.74 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 90 °C) δ 169.4, 169.4, 155.6, 137.9, 136.3, 128.5, 127.7, 127.6, 127.1, 127.1, 125.6, 66.1, 61.8, 50.7, 41.3, 35.0, 34.8, 31.9, 25.3, 24.2, 22.2, 22.0; IR ν 3320, 2400, 1676, 1526, 1473, 1427, 1214, 728, 671 cm^{-1}; MS m/z 470.2636 [$C_{26}H_{35}N_3O_5$ + H requires 470.2655] (base), 454, 426, 320, 303.

5-Methyl-(3*R*)-3-[(1*S*)-(1-methylcarbamoyl-2-phenylethylamino)methyl]hexanoic Acid Hydroxyl Amide (9). A mixture of **29** (165 mg, 0.351 mmol) in MeOH (3.5 mL) containing 5% Pd−$BaSO_4$ (75 mg) was stirred under a H_2 atmosphere (1 atm) at room temperature for 0.5 h. The catalyst was removed by filtration through a Celite pad, which was washed with MeOH (2 × 5 mL). The combined filtrates were concentrated under reduced pressure, and the resulting light yellow solid was purified by flash chromatography eluting with CH_2Cl_2/MeOH (9:1) to yield 111 mg (94%) of **9** as a white solid: mp 119 °C dec; ^{1}H NMR (CD_3OD) δ 7.30−7.19 (comp, 5 H), 3.20 (dd, J = 8.2, 5.9 Hz, 1 H), 2.98 (dd, J = 13.5, 5.9 Hz, 1 H), 2.75 (dd, J = 13.5, 8.2 Hz, 1 H), 2.70 (s, 3 H), 2.43 (dd, J = 11.8, 4.6 Hz, 1 H), 2.31 (dd, J = 11.8, 5.6 Hz, 1 H), 2.08 (dd, J = 15.7, 9.6 Hz, 1 H), 2.00−1.94 (comp, 2 H), 1.46−1.38 (m, 1 H), 1.07−0.95 (m, 2 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.77 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 177.1, 172.3, 139.1, 130.2, 129.6, 127.8, 65.9, 52.3, 42.7, 40.5, 37.4, 34.6, 26.2, 26.0, 23.3, 22.9; IR (Nujol) ν 3321, 3165, 2473, 2309, 1650, 1633,

1556, 1407, 1329, 700 cm^{-1}; MS *m/z* 336.2271 [$C_{18}H_{29}N_3O_5$ + H requires 336.2287] (base), 320, 303, 179.

3-(4-Methoxyphenyl)-(2*Z*)-propen-1-ol (31). A solution of $NaBH_4$ (171 mg, 4.5 mmol) in 0.1 N ethanolic NaOH (4.6 mL) was added dropwise to a stirred suspension of $Ni(OAc)_2 \cdot 4H_2O$ (1.15 g, 4.6 mmol) in EtOH (14 mL), and the mixture was stirred under argon at room temperature for 1 h. The mixture was stirred under H_2 (1 atm), and ethylenediamine (0.60 mL, 9.0 mmol) was added dropwise. A solution of 3-(4-methoxyphenyl)-2-propyn-1-ol[36] (5.02 g, 31.0 mmol) in EtOH (25 mL) was added, and the reaction was stirred under H_2 (1 atm) until 695 mL (31.0 mmol) of H_2 was absorbed (3 days). A mixture of pentane/Et_2O (1:1, 100 mL) was added, and the solids were removed by filtration through a pad of Florisil, which was rinsed with pentane/Et_2O (1:1, 5 × 100 mL). The combined filtrates and washings were concentrated under reduced pressure, and the resulting yellow solid was purified by recrystallization (CH_2Cl_2/pentane) to give **31** as pale yellow plates (first crop, 2.78 g; second crop, 1.49 g; 84% total yield): mp 45−50 °C; ^{1}H NMR δ 7.10 (d, J = 8.7 Hz, 2 H), 6.39 (d, J = 8.7 Hz, 2 H), 6.39 (d, J = 11.8 Hz, 1 H), 5.76 (dt, J = 6.1, 11.8 Hz, 1 H), 4.40 (dd, J = 6.1, 1.8 Hz, 2 H), 3.71 (s, 3 H); ^{13}C NMR δ 158.8, 130.6, 130.1, 129.4, 129.2, 113.7, 59.7, 55.3; IR ν 3612, 2955, 1602, 1572, 1508, 1467 cm^{-1}; MS *m/z* 164.0834 [$C_{10}H_{12}O_2$ requires 164.0837], 254, 147 (base).

3-(4-Methoxyphenyl)-(2*Z*)-propenyl Diazoacetate (32). A solution of the tosylhydrazone of glyoxylic acid chloride (9.3 g, 36 mmol), **31** (3.25 g, 19.8 mmol); *N*,*N*-dimethylaniline (4.8 mL, 38 mmol) in CH_2Cl_2 (50 mL) was stirred at 0 °C for 10 min, whereupon Et_3N (15 mL, 108 mmol) was added. The solution was stirred for 15 min at 0 °C and then overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (15:1) to give 3.00 g (65%) of **32** as a bright yellow oil: ^{1}H NMR δ 7.15 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.59 (d, J = 11.8 Hz, 1 H), 5.71 (dt, J = 6.6, 11.8 Hz, 1 H), 4.92 (dd, J = 1.4, 6.6 Hz, 2 H), 4.77 (br s, 1 H), 3.79 (s, 3 H); ^{13}C NMR δ 158.9, 133.3, 129.9, 128.5, 123.8, 113.7, 61.7, 55.1, 46.1; IR ν 3022, 2959, 2114, 1690, 1608 cm^{-1}; MS *m/z* 232.0850 [$C_{12}H_{12}N_2O_3$ requires 232.0848], 155 (base).

[1*S*-(1α,5α,6α)]-6-(4-Methoxyphenyl)-3-oxabicyclo[3.1.0]-hexan-2-one (33). A solution of **32** (1.32 g, 5.68 mmol) in CH_2Cl_2 (20 mL) was added via a syringe pump over 18 h to a solution of Rh_2[5(*S*)-MEPY]$_4$ (52.8 mg, 0.057 mmol) in CH_2Cl_2 (350 mL) under reflux. The reaction was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 720 mg (62%) of **33** as a white crystalline solid: mp 102−103 °C; ^{1}H NMR δ 7.23 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.35 (dd, J = 5.1, 4.5 Hz, 1 H), 4.04 (d, J = 9.6 Hz, 1 H), 3.78 (s, 3 H), 2.70 (app t, J = 8.4 Hz, 1 H), 2.58−2.50 (comp, 2 H); ^{13}C NMR δ 174.9, 159.1, 130.5, 124.1, 114.3, 65.8, 55.2, 25.5, 24.0, 23.6; IR ν 2967, 1760, 1613, 1580, 1515, 1474 cm^{-1}; MS *m/z* 205.0864 [$C_{12}H_{12}O_3$ + H requires 205.0865], 160 (base).

[1*S*-(1α,2α,3α)]-2-Hydroxymethyl-3-(4-methoxyphenyl)-1-*N*-methoxy-*N*-methyl Cyclopropyl Amide. A solution of Me_3Al (2 N in hexanes) (1 mL, 2 mmol) was slowly added dropwise to a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (149 mg, 1.52 mmol) in CH_2Cl_2 (2.8 mL), and the mixture was stirred at room temperature for 45 min. A solution of **33** (77 mg, 0.38 mmol) in CH_2Cl_2 (1.9 mL) was added dropwise, and the reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C; 1 N aqueous HCl (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 96 mg (94%) of a pale yellow oil that was used without further purification: ^{1}H NMR δ 7.03 (d, J = 8.8 Hz, 2 H), 6.75 (d, J = 8.8 Hz, 2 H), 3.92 (dd, J = 6.2, 5.5 Hz, 1 H), 3.80 (dd, J = 11.7 Hz, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.21 (s, 3 H), 2.71 (app t, J = 8.5 Hz, 1 H), 2.47−2.34 (m, 1 H), 1.86 (m, 1 H); ^{13}C NMR δ 158.1, 130.4, 127.0, 113.6, 61.1, 59.0, 55.0, 32.7, 27.5, 27.5, 25.2, 21.3; IR ν 3506, 2943, 1655, 1608, 1514, 1461, 1038 cm^{-1}; MS *m/z* 266.1407 [$C_{14}H_{19}NO_4$ + H requires 266.1392], 250 (base), 232, 144.

[1*R*-(1α,2α,3α)]-2-(4-Methoxyphenyl)-3-triisopropylsilyloxymethyl-1-*N*-methyl-*N*-methoxy Cyclopropyl Amide (34). A solution of the alcohol from the preceding experiment (268 mg, 1.0 mmol), 2,6-lutidine (180 μL, 2.5 mmol), and TIPSOTf (350 μL, 1.3 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 2 h, whereupon H_2O (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting clear oil was purified by flash chromatography eluting with hexanes/EtOAc (10:1) to give 360 mg (85%) of **34** as a clear oil: ^{1}H NMR δ 7.25 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7, 2 H), 4.17 (dd, J = 8.7, 11.2 Hz, 1 H), 4.07 (dd, J = 4.8, 11.2 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.12 (s, 3 H), 2.73 (app t, J = 8.9 Hz, 1 H), 2.55 (app t, J = 8.9 Hz, 1 H), 1.90−1.81 (m, 1 H), 1.18−1.03 (comp, 21 H); ^{13}C NMR δ 172.2, 158.7, 132.0, 127.6, 114.1, 62.1, 59.6, 55.7, 55.7, 27.9, 27.5, 20.3, 18.7, 12.6; IR ν 2943, 2866, 1658, 1612, 1514, 1464 cm^{-1}; MS *m/z* 422.2716 [$C_{23}H_{39}NO_4Si$ + H requires 422.2727], 378 (base), 248.

[1*R*-(1α,2β,3β)]-2-(4-Methoxyphenyl)-3-triisopropylsilyloxymethyl Cyclopropane-1-carboxylic Acid (35). Freshly sublimed *t*-BuOK (823 mg, 7.3 mmol) was added in one portion to a solution of **34** (387 mg, 0.92 mmol) in Et_2O (12 mL) at 0 °C. The suspension was allowed to warm to room temperature and stirred for 90 min, whereupon H_2O (16.5 μL, 0.92 mmol) was added dropwise. The reaction was stirred for another 15 min at room temperature, and 10% aqueous citric acid (15 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 310 mg (89%) of **35** as a clear oil: ^{1}H NMR δ 7.23 (d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 3.80 (s, 3 H), 3.62 (dd, J = 5.9, 10.7 Hz, 1 H), 3.42 (dd, J = 8.9, 10.7 Hz, 1 H), 2.90 (dd, J = 4.8, 9.3 Hz, 1 H), 2.12−2.16 (m, 1 H), 1.94 (app t, J = 4.8 Hz, 1 H), 1.03−0.94 (comp, 21 H); ^{13}C NMR δ 180.6, 159, 130.9, 128.0, 114.2, 61.8, 55.9, 31.7, 24.1, 18.5, 18.5, 12.5; IR ν 3148, 2944, 2866, 1896, 1612, 1515, 1463 cm^{-1}; MS *m/z* 379.2296 [$C_{21}H_{34}O_4Si$ + H requires 379.2304], 361, 335, 233, 205 (base).

[1*R*-(1α,2β,3β)]-(2-(4-Methoxyphenyl)-3-triisopropylsilyloxymethyl) Cyclopropane-1-*N*-alloxycarbonylamino-cyclopropane (36). Et_3N (100 μL, 0.72 mmol) was added dropwise to a solution of **35** (193 mg, 0.51 mmol) in acetone (3 mL) and H_2O (90 μL) at 0 °C. Ethyl chloroformate (70 μL, 0.73 mmol) was added; the solution was stirred at 0 °C for 30 min, and 4.3 N aqueous NaN_3 (180 μL, 0.77 mmol) was added. The mixture was stirred at 0 °C for an additional 2 h and then partitioned between Et_2O (3 mL) and H_2O (2 mL). The aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), and toluene (2 mL) was added. The Et_2O was removed under reduced pressure, and freshly distilled allyl alcohol (3 mL) was added. The mixture was heated at reflux for 3 h and then concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (8:1) to give 177 mg (80%) of **36** as a clear oil: ^{1}H NMR δ 7.35 (br s, 2 H), 6.80 (d, J = 8.7 Hz, 2 H), 5.94 (ddt, J = 15.9, 10.6, 5.5 Hz, 1H), 5.33 (d, J = 15.9 Hz, 1 H), 5.23 (d, J = 10.6 Hz, 1 H), 5.12 (br s, 1 H), 4.59−4.63 (m, 2 H), 3.79 (s, 3 H), 3.60−3.66 (m, 1 H), 3.40 (dd, J = 10.7, 7.7 Hz, 1 H), 2.82 (dd, J = 6.1, 3.9 Hz, 1 H), 2.35 (dd, J = 10.0, 3.9 Hz, 1 H), 1.62−1.52 (m, 1 H), 1.08−0.93 (comp, 21 H); ^{13}C NMR δ 158.3, 156.7 132.8, 130.7, 128.4, 117.7, 113.6, 65.6, 61.5, 55.3, 33.3, 29.7, 29.0, 17.9, 11.9; IR ν 3444, 2944, 2866, 1723, 1612, 1514 cm^{-1}; MS *m/z* 434.2723 [$C_{20}H_{39}NO_4Si$ + H requires 434.2727] (base), 390, 260, 246.

2-(*R*)-Isobutyl-4-*tert*-butylbutanoate Pentafluorophenyl Ester (38). A solution of pentafluorophenol (249 mg, 1.35 mmol) and DCC (91 mg, 0.44 mmol) in EtOAc (1.8 mL) was stirred at 0 °C for 30 min, and a solution of **37**[30] (0.44 mmol) in EtOAc (0.9 mL) was added. The mixture was stirred at 0 °C for 1 h and then overnight at room temperature. The

mixture was filtered through a Celite pad that was rinsed with EtOAc (2 × 3 mL), and the combined filtrate and washings were concentrated under reduced pressure. The resulting pale yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (10:1) to give 159 mg (91%) of **38** as a clear oil: ^{1}H NMR δ 3.26−3.15 (m, 1 H), 2.75 (dd, J = 9.3, 16.8 Hz, *1* H), 2.53 (dd, J = 5.2, 16.8, 1 H), 1.81−1.66 (m, 2 H), 1.49−1.38 (m, 1 H), 1.46 (s, 9 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 171.3, 170.2, 40.9, 39.5, 37.6, 27.9, 25.8, 22.6, 22.0; IR ν 2954, 1778, 1519, 1155, 1096, 1002 cm^{-1}; MS *m*/*z* 397.1434 [$C_{18}H_{21}F_5O_4$ + H requires 397.1438], 341, 323.

[1*R*-(1α,2*β*,3*β*)]-1-[(2-(*R*)-Isobutyl-4-*tert*-butoxycarboxyl)-butanoyl]Amino-3-(4-methoxyphenyl)-2-triisopropylsilyl-oxymethyl Cyclopropane (39). A solution of **36** (515 mg, 1.2 mmol), **38** (566 mg, 1.4 mmol), $(Ph_3P)_4Pd$ (28 mg, 0.024 mmol), and freshly distilled Bu_3SnH (380 mg, 1.3 mmol) in CH_2Cl_2 (2.4 mL) was heated under reflux overnight. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (15:1) to give 560 mg (84%) of **39** as a pale yellow syrup that crystallized upon prolonged standing under vacuum: mp 80−83 °C; ^{1}H NMR δ 7.32 (d, J = 8.8 Hz, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.01 (br s, 1 H), 3.74 (s, 3 H), 3.67 (dd, J = 5.8, 10.8 Hz, 1 H), 3.33 (dd, J = 8.4, 10.8 Hz, 1 H), 2.88 (dd, J = 4.0, 7.6 Hz, 1 H), 2.60−2.53 (comp, 2 H), 2.27 (dd, H = 12.4, 2.8 Hz, 1 H), 2.21 (dd, J = 4.0, 9.8 Hz, 1 H), 1.65 (ddd, J = 5.8, 9.0, 13.4 Hz, 1 H), 1.59−1.42 (m, 1 H), 1.55−1.49 (m, 1 H), 1.40 (s, 9 H), 1.16 (ddd, J = 5.2, 8.2, 13.4 Hz, 1 H), 0.97−0.93 (comp, 21 H), 0.90 (d, J = 6.62 Hz, 3 H), 0.88 (d, J = 6.62 Hz, 3 H); ^{13}C NMR δ 176.2, 172.0, 158.2, 130.8, 128.4, 113.5, 80.9, 61.6, 55.2, 41.4, 40.7, 38.5, 32.7, 29.5, 28.9, 28.0, 25.8, 23.0, 22.2, 17.9; IR ν 3438, 3014, 2958, 2867, 1718, 1673, 1514 cm^{-1}; MS *m*/*z* 562.3952 [$C_{32}H_{55}NO_5Si$ + H requires 562.3928], 521, 430, 391 (base), 176.

[1*S*-(1α,2*β*,3*β*)]-1-(3-(*R*)-Isobutylsuccinimido)-2-hydroxymethyl-3-(4-methoxyphenyl) Cyclopropane (42). A solution of **39** (717 mg, 1.3 mmol) in formic acid (13 mL) was stirred at room temperature for 1 h, and the reaction was concentrated under reduced pressure. The resulting oil was dissolved in AcCl (5.2 mL), and the solution was heated under reflux for 1 h. The mixture was concentrated under reduced pressure; the residual oil was dissolved in MeOH (50 mL), and the solution was heated under reflux for 1 h. The mixture was again concentrated under reduced pressure, and the resulting brown oil was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 286 mg (66%) of **42** as an off-white solid: mp 107−110 °C; ^{1}H NMR δ 7.25 (d, J = 8.7 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 2 H), 3.77−3.75 (m, 1 H), 3.75 (s, 3 H), 3.20 (dd, J = 9.2, 11.3 Hz, 1 H), 2.84−2.74 (comp, 3 H), 2.69 (app t, J = 4.3 Hz, 1 H), 2.34 (dd, J = 13.8, 3.2 Hz, 1 H), 1.83−1.69 (comp, 3 H), 1.33 (ddd, J = 5.6, 10.1, 15.5 Hz, 1 H), 0.95 (d, J = 5.6 Hz, 3 H), 0.89 (d, J = 5.6 Hz, 3 H); ^{13}C NMR δ 180.7, 176.9, 158.6, 130.3, 127.6, 113.9, 61.3, 55.2, 40.5, 38.0, 34.8, 32.5, 27.4, 27.3, 26.1, 22.9, 21.5; IR ν 3508, 3002, 2959, 2874, 1775, 1705, 1612, 1515 cm^{-1}; MS *m*/*z* 332.1856 [$C_{19}H_{25}NO_4$ + H requires 332.1862], 314 (base), 300, 156.

[1*S*-(1α,2*β*,2*β*)]-2-(3-(*R*)-Isobutylsuccinimido)-3-(4-methoxyphenyl) Cyclopropane Carboxaldehyde. A solution of **42** (96 mg, 0.29 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a stirred suspension of Dess−Martin periodinane (209 mg, 0.58 mmol) in CH_2Cl_2 (1.5 mL), and stirring was continued at room temperature for 30 min. A solution of 5% aqueous $NaHCO_3$ (3 mL) containing $Na_2S_2O_3$ (50 mg, 0.32 mmol) was added in one portion. Stirring was continued for 15 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give 92 mg (96%) of a white solid: mp 88−90 °C; ^{1}H NMR δ 9.12 (dd, J = 2.2, 5.0 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 2 H), 6.80 (d, J = 8.8 Hz, 2 H), 3.91 (dd, J = 5.0, 10.2 Hz, 1 H), 3.75 (s, 3 H), 3.39 (dd, J = 5.8, 10.2 Hz, 1 H), 2.88−2.76 (comp, 3 H), 2.34 (d, J = 13.5 Hz, 1 H), 1.82−1.77 (m, 1 H), 1.75−1.67 (m, 1 H), 1.37−1.31 (m, 1 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 197.6, 179.8, 176.0, 160.0, 130.4, 125.4, 114.0, 55.2, 40.5, 38.0, 34.7, 34.0, 30.9, 26.0, 22.9, 21.5; IR ν 2960, 2839, 1712, 1613, 1516 cm^{-1}; MS *m*/*z* 330.1708 [$C_{19}H_{23}NO_4$ + H requires 330.1705], 175 (base), 156.

[1*S*-(1α,2*β*,2*β*)]-2-(3-(*R*)-Isobutylsuccinimido)-3-(4-methoxyphenyl) Cyclopropane Carboxylic Acid (43). A solution of 0.1 M aqueous $NaClO_2$ (13 mL, 1.3 mmol) was added dropwise over 1.5 h to a solution of aldehyde from the preceding experiment (299 mg, 0.91 mmol) in MeCN (9 mL) containing 0.65 M aqueous NaH_2PO_4 (3.6 mL) and 30% aqueous H_2O_2 (0.23 mL, 2.2 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h, and sodium sulfite (50 mg, 0.40 mmol) was added. The mixture was acidified to pH = 4 by adding 1 N aqueous HCl and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting pale yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 301 mg (96%) of **43** as a pale yellow foam: mp 128−131 °C; ^{1}H NMR δ 9.43 (br s, 1 H), 7.26 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 3.78 (s, 3 H), 3.69 (dd, J = 4.5, 5.9 Hz, 1 H), 3.16 (dd, J = 5.9, 10.3 Hz, 1 H), 2.88−2.80 (comp, 2 H), 2.71 (app dt, J = 10.3, 4.5 Hz, 1 H), 2.35 (dd, J = 13.4, 8.0 Hz, 1 H), 1.84−1.70 (comp, 2 H), 1.40−1.32 (m, 1 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 108.7, 176.9, 174.8, 159.4, 130.8, 126.2, 114.3, 55.8, 41.1, 38.5, 35.4, 35.3, 31.1, 26.9, 26.6, 23.6, 22.1; IR ν 3092, 2961, 2872, 2839, 1712, 1614, 1517 cm^{-1}; MS *m*/*z* 346.1652 [$C_{19}H_{23}NO_5$ + H requires 346.1654], 328 (base), 173.

[1*S*-(1α,2*β*,3*β*)]-2-Allyloxycarbonylamino-1-(3-(*R*)-isobutylsuccinimido)-3-(4-methoxyphenyl) Cyclopropane (44). Et_3N (37 μL, 0.26 mmol) was added dropwise to a solution of **43** (65 mg, 0.19 mmol) in acetone (1 mL) containing H_2O (35 μL) at 0 °C. Ethyl chloroformate (20 μL, 0.26 mmol) was added, and the mixture was stirred at 0 °C for 30 min. A solution of 4.3 M aqueous sodium azide (66 μL, 0.28 mmol) was added, and stirring was continued at 0 °C for 2 h. The reaction mixture was partitioned between H_2O (1 mL) and CH_2Cl_2 (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried ($MgSO_4$); toluene (1 mL) was added, and the CH_2Cl_2 was removed under reduced pressure. Allyl alcohol (2 mL) was added, and the mixture was heated at reflux for 4 h. The mixture was concentrated under reduced pressure, and the resulting amber oil was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to afford 62 mg (81%) of **44** as a white solid: mp 113−117 °C; ^{1}H NMR δ 7.22 (br d, J = 8.7 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 2 H), 5.93−5.79 (m, 1 H), 5.23 (d, J = 18.4 Hz, 1 H), 5.18 (d, J = 10.9 Hz, 1 H), 4.56−4.05 (comp, 3 H), 3.76 (s, 3 H), 3.76−3.73 (m, 1 H), 3.32−3.25 (m, 1 H), 3.01 (dd, J = 5.6, 8.6 Hz, 1 H), 2.83−2.76 (comp, 2 H), 2.32 (dd, J = 7.7, 13.3 Hz, 1 H), 1.82−1.77 (m, 1 H), 1.73−1.68 (m, 1 H), 1.33 (ddd, J = 5.5, 8.0, 10.2 Hz, 1 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 180.1, 176.3, 158.9, 156.2, 132.6, 130.2, 125.3, 117.8, 114.1, 65.7, 55.2, 40.5, 38.0, 35.6, 34.8, 33.6, 27.2, 26.1, 26.1, 23.0, 21.5; IR ν 3686, 3021, 2962, 1710, 1602, 1516 cm^{-1}; MS *m*/*z* 401.2072 [$C_{22}H_{28}N_2O_5$ + H requires 401.2076], 343, 300, 184, 156 (base).

[1*S*-(1α,2*β*,3*β*)]-2-Acetamido-1-(3-(*R*)-isobutylsuccinimido)-3-(4-methoxyphenyl) Cyclopropane (45). $(Ph_3P)_4Pd$ (8 mg, 0.0069 mmol) and Bu_3SnH (100 μL, 0.37 mmol) were added to a solution of **44** (131 mg, 0.33 mmol) in CH_2Cl_2 (3.3 mL) containing Ac_2O (65 μL, 0.69 mmol) at room temperature. The mixture was stirred at room temperature for 15 min and then concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give a white solid that was recrystallized from benzene to give 99 mg (84%) of **45** as a white solid: mp 135−139 °C; ^{1}H NMR (C_5D_5N) δ 9.07 (br s, 1 H), 7.59 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 4.31 (m, 1 H), 3.62 (s, 3 H), 3.51 (dd, J = 3.5, 5.0 Hz, 1 H), 3.11 (dd, J = 5.0, 7.7 Hz, 1 H), 2.90−2.76 (comp, 2 H), 2.40 (d, J = 13.4 Hz, 1 H), 1.90 (s, 3 H), 1.80 (ddd, J = 4.5, 8.6, 13.3 Hz, 1 H), 1.61 (m, 1 H), 1.27 (m, 1 H), 0.82 (d, J = 6.6 Hz, 3 H), 0.76 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 180.7, 177.0, 171.4, 159.1, 131.2, 127.9, 114.2, 55.2, 40.4, 38.4,

35.2, 35.1, 34.1, 29.3, 26.2, 23.1, 22.7, 21.6; IR ν 3428, 3026, 2974, 1709, 1516, 1402 cm^{-1}; MS *m*/*z* 359.1966 [$C_{20}H_{26}N_2O_4$ + H requires 359.1971], 291, 279, 206.

[1*S*-(1*β*,2α,3α)]-2-Acetamido-1-[(2-(*R*)-isobutyl-4-hydroxycarboxamido)butanoyl]amino-3-(4-methoxyphenyl) Cyclopropane (10). A solution of 2 M methanolic KOH (0.5 mL) was added with stirring to a solution of 1 M methanolic $HONH_2$·HCl (0.75 mL), which was prepared from freshly recrystallized $HONH_2$·HCl (MeOH). The mixture was allowed to stand until the precipitated KCl settled. A portion (0.42 mL) of the resulting solution was added dropwise to a solution of **45** (30 mg, 0.084 mmol) in MeOH (0.42 mL) at room temperature. After 20 min, H_2O (1.5 mL), saturated aqueous Na_2CO_3 (0.2 mL), and EtOAc (2 mL) were added. The layers were separated, and the organic layer was extracted with H_2O (2 × 2 mL). The combined aqueous layers were acidified with 6 N aqueous HCl, saturated with solid NaCl, and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 25 mg (76%) of a mixture of the isomeric hydroxamic acids **10** and **46** as a clear glass. The desired hydroxamic acid **10** was isolated by preparative TLC, eluting three times with EtOAc/MeOH/AcOH (42:2:1), as the less polar isomer (7.5 mg, 30% of crude mixture): ^{1}H NMR (DMSO-d_6) δ 10.39 (br s, 1 H), 8.76 (br s, 1 H), 8.30 (d, J = 3.8 Hz, 1 H), 7.95 (d, J = 4.8 Hz, 1 H), 7.09 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 8.6 Hz, 2 H), 3.70 (s, 3 H), 3.11 (dd, J = 4.4, 8.4 Hz, 1 H), 3.02 (app dt, J = 8.4, 4.4 Hz, 1 H), 2.68−2.60 (m, 1 H), 2.16−2.08 (comp, 2 H), 1.96 (dd, J = 7.4, 14.2 Hz, 1 H), 1.62 (s, 3 H), 1.48−1.39 (comp, 2 H), 1.07−1.02 (m, 1 H), 0.86 (d, J = 6.2 Hz, 3 H), 0.80 (d, J = 6.2 Hz, 3 H); ^{13}C NMR δ 175.0, 170.1, 167.2, 157.6, 129.5, 127.9, 113.3, 54.9, 41.0, 35.6, 33.6, 30.3, 25.5, 22.2, 21.8, 20.9; IR ν 3684, 3617, 3421, 3282, 3019, 2796, 2899, 1713, 1666, 1613, 1515 cm^{-1}; MS *m*/*z* 392.2183 [$C_{20}H_{29}N_3O_5$ + H requires 392.2185], 359, 343, 279, 221, 204, 172 (base).

***N*-[(1*S*)-2-Azido-1-(4-methoxyphenylmethyl)ethyl](*tert*-butoxy)carboxamide (48).** Freshly distilled methanesulfonyl chloride (865 μL, 11.2 mmol) was added dropwise to a stirred solution of **47**[44] (2.10 g, 7.45 mmol) and Et_3N (1.31 mL, 11.9 mmol) in CH_2Cl_2 (250 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. The mixture was washed with H_2O (100 mL) and brine (100 mL), and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mesylate was dissolved in DMF (75 mL); solid NaN_3 (2.44 g, 37.3 mmol) was added, and the mixture was stirred at 60 °C for 4 h. The DMF was removed under reduced pressure, and the residue was partitioned between H_2O (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to yield 1.64 g (72%) of **48** as a white solid: mp 59−60 °C; ^{1}H NMR δ 7.08 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.69−4.58 (m, 1 H), 3.94−3.85 (m, 1 H), 3.76 (s, 3 H), 3.38 (br dd, J = 12.2, 3.7 Hz, 1 H), 3.27 (dd, J = 12.2, 4.5 Hz, 1 H), 2.79 (br dd, J = 13.8, 5.8 Hz, 1 H), 2.69 (dd, J = 13.8, 8.0 Hz, 1 H), 1.40 (s, 9 H); ^{13}C NMR δ 158.4, 155.1, 130.2, 129.0, 114.1, 79.7, 55.2, 53.0, 51.4, 37.2, 28.3; IR ν 3438, 2104, 1706, 1504, 1245, 1168 cm^{-1}; MS *m*/*z* 307.1773 [$C_{15}H_{22}N_4O_3$ + H requires 307.1770], 251 (base), 207.

***N*-(2*S*)-2-[(*tert*-Butoxycarbonylamino)-3-(4-methoxyphenyl)propyl]acetamide.** A solution of **48** (1.57 g, 5.12 mmol) in Ac_2O (100 mL) containing 10% Pd−C (545 mg) was stirred under H_2 (1 atm) at room temperature for 5 h. The excess Ac_2O was removed under reduced pressure, and the residue was dissolved in MeOH (50 mL). The catalyst was removed by vacuum filtration through a Celite pad that was washed with MeOH (2 × 25 mL). The combined filtrate and washings were concentrated under reduced pressure, and the resulting solid was recrystallized from *i*-PrOH/heptanes to yield 1.22 g (74%) of a white solid: mp 130−131 °C; ^{1}H NMR δ 7.08 (d, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 6.13−6.05 (m, 1 H), 4.78−4.68 (m, 1 H), 3.85−3.80 (m, 1H), 3.76 (s, 3 H), 3.33−3.19 (m, 2 H), 2.78 (br dd, J = 7.5, 5.6 Hz, 1 H), 2.66 (dd, J = 14.0, 7.5 Hz, 1 H), 1.93 (s, 3H), 1.39 (s, 9 H); ^{13}C NMR δ 170.7, 158.4, 156.5, 130.2, 129.1, 114.1, 79.7, 55.3, 52.1, 44.1, 38.3, 28.3, 23.2; IR ν 1596, 1511, 1368, 1245, 1169, 1037 cm^{-1}; MS *m*/*z* 323.1978 [$C_{17}H_{26}N_2O_4$ + H requires 323.1971], 295, 267, 223 (base).

***N*-[(2*S*)-2-Amino-3-(4-methoxyphenyl)propyl]acetamide Hydrochloride (49).** A solution of the carbamate from the preceding experiment (1.02 g, 3.16 mmol) in 1 M methanolic HCl (50 mL) was stirred at room temperature for 45 min, whereupon the solvent was removed under reduced pressure. The resulting solid was recrystallized from *i*-PrOH/heptanes to give 659 mg (81%) of the hydrochloride salt of **49** as a white solid (mp 191−195 °C) that contained a minor impurity (<3% by ^{1}H NMR). An analytical sample of the free base was obtained by dissolving a small sample (30 mg) of **49** in saturated aqueous $NaHCO_3$ (2 mL) and extracting the solution with CH_2Cl_2 (4 × 4 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (1:4) to yield 21 mg (80%) of the free amine as a white solid: mp 95−97 °C; ^{1}H NMR δ 7.06 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.10−6.04 (m, 1 H), 3.77 (s, 3 H), 3.43 (ddd, J = 12.9, 6.1, 3.6 Hz, 1 H), 3.07−2.97 (comp, 2 H), 2.73 (dd, J = 13.7, 4.6 Hz, 1 H), 2.41 (dd, J = 13.7, 8.2 Hz, 1 H), 1.97 (s, 3 H); ^{13}C NMR δ 170.2, 158.3, 130.3, 130.1, 114.0, 55.2, 52.4, 45.2, 41.8, 23.3; IR ν 3436, 3370, 1663, 1612, 1513, 1248, 1178, 1036, 809 cm^{-1}; MS *m*/*z* 223.1447 [$C_{12}H_{18}N_2O_2$ + H requires 223.1447] (base), 206.

(3*R*)-3-[2-Acetylamino-(1*S*)-1-(4-methoxybenzyl)ethylcarbamoyl]-5-methylhexanoic Acid *tert*-Butyl Ester (51). A solution of isobutyl chloroformate (206 μL, 1.59 mmol), **37**[30] (305 mg, 1.32 mmol), and *N*-methylmorpholine (204 μL, 1.85 mmol) in THF (6.6 mL) at −10 °C was stirred for 1 h at −10 °C. The amine hydrochloride **49** (411 mg, 1.59 mmol) was then added, and the mixture was stirred at room temperature overnight. The THF was removed under reduced pressure, and the residue was dissolved in EtOAc (15 mL). The organic solution was washed with 10% aqueous citric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (3:2) to yield 462 mg (81%) of **51** as a white solid: mp 133−134 °C; ^{1}H NMR δ 7.10 (d, J = 8.6 Hz, 2 H), 6.80 (d, J = 8.6 Hz, 2 H), 6.37−6.31 (m, 1 H), 6.09 (d, J = 7.1 Hz, 1 H), 4.01−3.97 (m, 1 H), 3.76 (s, 3 H), 3.40−3.32 (m, 2 H), 2.91 (dd, J = 13.9, 6.8 Hz, 1 H), 2.66 (dd, J = 13.9, 7.3 Hz, 1 H), 2.53−2.47 (comp, 2 H), 2.27 (dd, J = 20.5, 8.5 Hz, 1 H), 1.93 (s, 3 H), 1.53−1.37 (comp, 2 H), 1.41 (s, 9 H), 1.15−1.09 (m, 1 H), 0.83 (d, J = 5.2 Hz, 3 H), 0.82 (d, J = 5.3 Hz, 3 H); ^{13}C NMR δ 175.8, 172.0, 171.0, 158.4, 130.1, 129.5, 114.0, 80.9, 55.2, 52.3, 43.0, 41.4, 41.3, 38.3, 37.5, 28.1, 25.7, 23.1, 22.9, 22.2; IR ν 1717, 1663, 1514, 1246, 1216, 1156 cm^{-1}; MS *m*/*z* 435.2858 [$C_{24}H_{38}N_2O_5$ + H requires 435.2859] (base), 379.

(3*R*)-3-[2-Acetylamino-(1*S*)-1-(4-methoxybenzyl)ethylcarbamoyl]-5-methylhexanoic Acid. A solution of **51** (245 mg, 0.563 mmol) in a mixture of CF_3CO_2H (5.6 mL) and CH_2Cl_2 (5.6 mL) was stirred at room temperature for 2 h. Toluene (5 mL) was added, and the solution was concentrated under reduced pressure. The residual CF_3CO_2H was removed by azeotropic distillation with toluene (2 × 5 mL) to give a yellow oil that was purified by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) to yield 188 mg (88%) of a white solid: mp 92−94 °C; ^{1}H NMR (CD_3OD) δ 7.13 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 4.12−4.08 (m, 1 H), 3.74 (s, 3 H), 3.29 (dd, J = 13.7, 9.0 Hz, 1 H), 3.23 (dd, J = 13.7, 4.9 Hz, 1 H), 2.72 (d, J = 7.2 Hz, 2 H), 2.67−2.63 (m, 1 H), 2.37 (dd, J = 16.4, 8.1 Hz, 1 H), 2.25 (dd, J = 16.4, 6.2 Hz, 1 H), 1.90 (s, 3 H), 1.49−1.37 (comp, 2 H), 1.17−1.11 (m, 1 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 177.6, 175.5, 173.6, 159.8, 131.4, 131.3, 114.8, 55.6, 52.5, 43.5, 42.7, 42.4, 38.5, 38.1, 26.9, 23.5, 22.7, 22.4; IR ν 1714, 1661, 1513, 1248 cm^{-1}; MS *m*/*z* 379.2247 [$C_{20}H_{30}N_2O_5$ + H requires 379.2233), 361 (base), 223.

***N*-1-[2-Acetylamino-(1*S*)-1-(4-methoxybenzyl)ethyl]-*N*-4-hydroxy-(2*S*)-2-isobutylsuccinamide (11).** A solution of

acid from the preceding experiment (169 mg, 0.447 mmol), isobutyl chloroformate (70 μL, 0.536 mmol), and *N*-methylmorpholine (69 μL, 0.625 mmol) in THF (2.2 mL) was stirred at −10 °C for 0.5 h, whereupon *O*-(trimethylsilyl)hydroxylamine (66 μL, 0.536 mmol) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a Celite pad that was washed with MeOH (2 × 5 mL). The combined filtrate and washings were concentrated under reduced pressure, and the resulting light yellow solid was recrystallized from THF to yield 160 mg (91%) of **11** as a white solid: mp 134 °C dec; ^{1}H NMR (CD_3OD) δ 7.12 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 4.13−4.08 (m, 1 H), 3.73 (s, 3 H), 3.28−3.26 (m, 2 H), 2.75 (dd, J = 14.1, 6.6 Hz, 1 H), 2.70 (dd, J = 14.1, 8.5 Hz, 1 H), 2.68−2.63 (m, 1 H), 2.07 (dd, J = 14.4, 7.1 Hz, 1 H), 1.99 (dd, J = 14.4, 7.5 Hz, 1 H), 1.91 (s, 3 H), 1.50−1.44 (m, 1 H), 1.40−1.35 (m, 1 H), 1.09−1.03 (m, 1 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 177.2, 173.6, 170.6, 159.8, 131.4, 131.3, 114.8, 55.7, 52.4, 43.6, 42.7, 42.1, 38.5, 37.1, 26.9, 23.8, 22.7, 22.2; IR (Nujol) ν 3216, 1660, 1614, 1556, 1514, 1302, 1242, 1183, 1030, 818 cm^{-1}; MS m/z 394.2348 [$C_{20}H_{31}N_3O_5$ + H requires 394.2342], 362 (base), 352, 225, 172.

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Supporting Information Available: NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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