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Articles

Activated Ketone Based Inhibitors of Human Renin

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Application of the concept of activated ketones to the design of novel and potent transition-state analog inhibitors of the aspartyl protease renin is described. Three different classes of peptidic activated ketones were synthesized: 1,1,1-trifluoromethyl ketones, α-keto esters, and α-diketones. The corresponding alcohols were also evaluated as renin inhibitors in each series. While the trifluoromethyl alcohol **12** (I_{50} = 4000 nM) was equipotent to the simple methyl alcohol **7** (I_{50} = 3200 nM), the structurally similar α-hydroxy esters (**32** and **30**, I_{50}'s = 5.3 and 4.7 nM, respectively) and α-hydroxy ketones (**41** and **42**, I_{50} = 23 and 15 nM, respectively) were 150–300-fold more active. The hydrating capability of the activated ketone functionality was important for intrinsic potency in the case of trifluoromethyl ketones, as illustrated by the significantly better activity of trifluoromethyl ketone **13** (I_{50} = 250 nM) compared to its alcohol analog **12** (I_{50} = 4000 nM). It was however unimportant for the α-keto ester (**20** and **31**, I_{50} = 15 and 4.1 nM, respectively) and α-diketone (**43** and **44**, I_{50} = 52 and 28 nM, respectively) based inhibitors, since their activity was essentially similar to that of the corresponding alcohols. These results collectively suggest that, whereas the trifluoromethyl ketones derive their renin inhibitory potency primarily from their ability to become hydrated, this is not a critical feature for the activity of α-dicarbonyl-based inhibitors. The α-keto ester and α-diketone based renin inhibitors benefit predominantly from the hydrophobic and/or H-bonding type binding interactions of the neighboring ester or acyl group itself, rather than the ability of this group to deactivate the adjacent ketone group and thereby make it susceptible to hydration.

Introduction

Renin is an aspartyl protease that cleaves angiotensinogen to the decapeptide angiotensin I, which in itself is inactive but is hydrolyzed by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II, a potent vasoconstrictor and stimulant of aldosterone secretion. Captopril, the first orally active ACE inhibitor, has demonstrated that interruption of the renin–angiotensin system is of therapeutic benefit in hypertension and congestive heart failure.[1] Inhibitors of renin would be expected to produce the same result and therefore might constitute a novel alternative to ACE inhibitors. This has resulted in intensive research in this area in several laboratories over the last decade.[2]

Activated ketone based inhibitors have found application for all of the four different classes of proteases.[3] This versatility arises from the fact that they exist as hydrates in aqueous media and can thus directly serve as transition-state analogs and/or they can react with a nucleophilic residue (e.g. serine hydroxyl or cysteine thiol) to form a reversible, hemiacetal-type intermediate (Scheme I). Either pathway leads to mimics of the tetrahedral intermediate formed during peptide-bond hydrolysis and thus, such compounds can be viewed as transition-state-analog inhibitors. Very elegant applications of this simple yet powerful concept were originally demonstrated by Abeles

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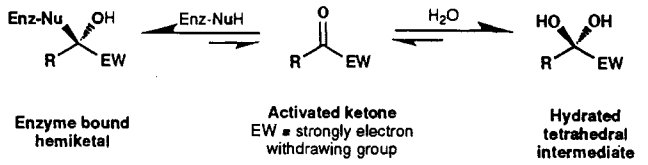
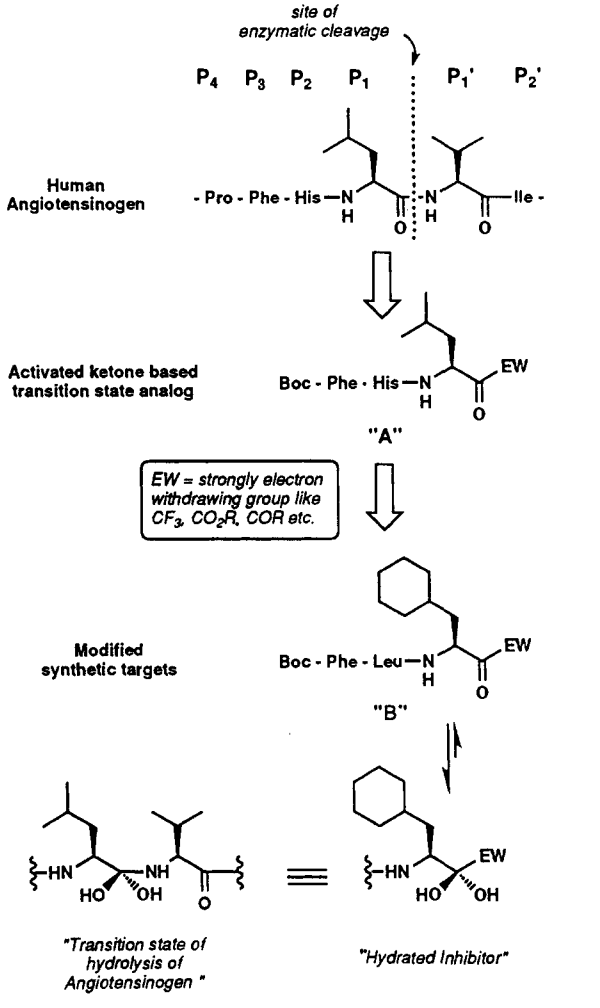
Scheme I



Scheme II. Design of Activated Ketone Based Renin Inhibitors



and co-workers by making fluoro ketone based proteinase inhibitors.[4]

During our efforts in the renin program, we investigated the application of this principle in the design of novel renin inhibitors. Thus, insertion of an activated ketone functionality at the site of enzymatic cleavage (P_1–P_1' Leu–Val linkage) in a human renin substrate analog could potentially mimic the transition state of this reaction (Scheme II). Specifically, the investigation of three classes of activated ketones, namely the 1,1,1-trifluoromethyl ketones, α-keto esters, and α-diketones was undertaken in this study. For synthetic simplicity, histidine at the P_2 position of human renin sequence was replaced by leucine in our initial studies since the activated ketone functionality may not be compatible with a basic functional group within the same molecule (*vide infra*). Such a replacement has now been reported to be acceptable for several classes of renin inhibitors.[2,5-8] For enhanced potency, the isobutyl side chain of leucine at P_1 was replaced by a cyclohexylmethyl group, a substitution that usually leads to dramatic levels of improvement in the potency of renin inhibitors.[2,9]

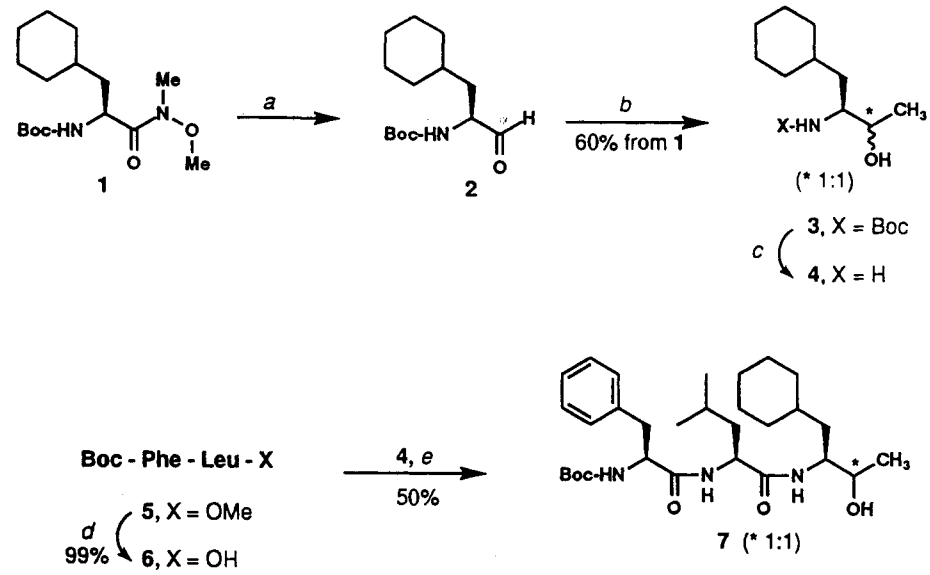
Chemistry

Preparation of the Baseline Compound 7. The α-amino aldehyde **2** was best prepared by $LiAlH_4$ treatment of the Weinreb amide **1**[10] and used directly without any further purification[11] (Scheme III). Prolonged storage of **2** was avoided to prevent possible epimerization of this sensitive molecule.[12] Treatment of **2** with MeMgBr afforded a 1:1 mixture of the amino alcohols **3**. Deprotection to **4** followed by coupling with the dipeptide **6** yielded the alcohol **7**.

Preparation of the Trifluoromethyl Ketone 13.[13] At the outset of this project, no general method existed for the synthesis of peptidic trifluoromethyl ketones like **13**. Having decided to prepare **13** from its alcohol precursor **12**, the main task was to prepare the trifluoromethyl amino alcohol **11**. We reasoned that **11** could be prepared by Curtius rearrangement of the appropriately protected carboxylic acid such as **9**. Alternatively, one can also utilize the nitro group as an amine equivalent to arrive at an intermediate such as **11**, an approach that has been independently disclosed by Abeles[14] and Trainor.[15] Thus, condensation of the dianion of 3-cyclohexyl propionic acid with trifluoroacetaldehyde generated *in situ* from its ethyl hemiacetal[16] yielded the β-hydroxy acid **8** as a racemic mixture of *erythro* and *threo* isomers in 67% yield (Scheme IV). The alcohol was protected as the silyl ether **9** in essentially quantitative yields. The Curtius rearrangement of **9** utilizing diphenylphosphoryl azide (DPPA) deserves some comments.[17] In our observation, it proceeds more efficiently in a nonpolar solvent such as hexane despite the initial immiscibility of the carboxylic acid. For example, under identical conditions, rearrangement of acid **9** in hexane and THF afforded the amine **10** in 75% and 41% yields, respectively. A second critical feature of this reaction is the presence of excess base. Thus, a mixture of the acid **9**, DPPA, and triethylamine (1.0 equiv) in hexane was refluxed for 3 h, at which stage complete isocyanate formation was indicated by IR (C=O at 2250 cm^{-1}). After addition of benzyl alcohol to the refluxing solution, very little reaction was observed even after an additional 2 h. However, upon the addition of another equivalent of triethylamine, immediate product formation was revealed by TLC. The reaction was left for overnight reflux and after purification, afforded the rearranged product in 75% overall yield. Intermediate **10** was completely deprotected[18] and the amine was cleanly isolated as its tosylate salt **11** in 85% overall yield from **10**. DCC/HOBt coupling of **11** with the dipeptide acid **6** afforded the trifluoromethyl alcohol **12** in 75% yield as a 1:1.5:2.7:2.7 mixture of four diastereomers as determined by HPLC. Dess–Martin periodinane[19] proved to be the reagent of choice for the oxidation of tripeptidic trifluoromethyl alcohol **12** to the ketone **13**.[20]

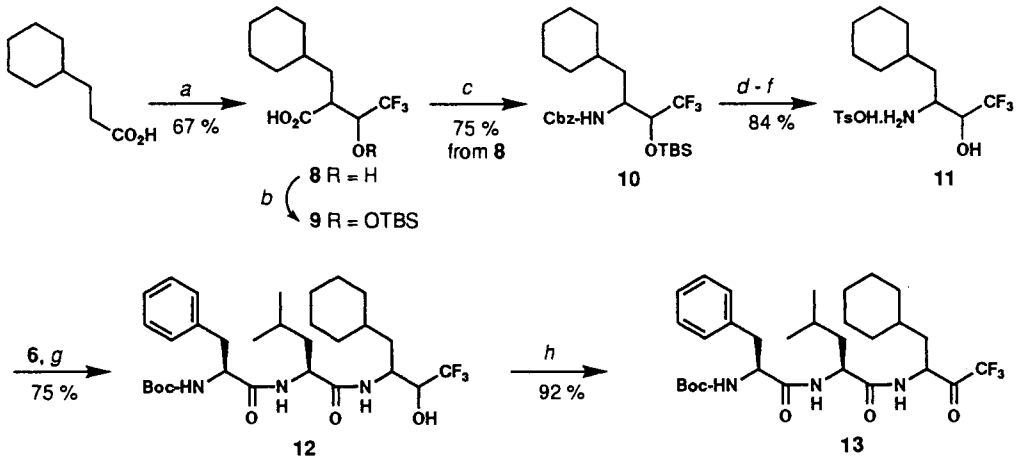
Preparation of α-Keto Esters. Preparation of peptidic α-keto esters was pursued by two routes (Scheme V). First, a nonchiral synthesis via a modified Dakin–West reaction[21] was undertaken and this was later followed by an investigation of new routes for the chiral synthesis of such compounds. Thus, the tripeptide **19**, prepared by straightforward coupling and deprotections, was subjected to the modified Dakin–West reaction.[22] Although our initial attempts were less rewarding (11% yield of **20**), substantial improvement was realized when freshly distilled oxalyl chloride and an excess of base (5.0 equiv pyridine) were employed for the reaction, and if the enol anhydride formed

Scheme III. Preparation of Baseline Compound[a]



[a] Reagents: (a) $LiAlH_4$, Et_2O; (b) MeMgBr, THF; (c) anhydrous HCl in EtOAc; (d) 1 N NaOH, MeOH; (e) **4** and **6**, DCC, HOBt, iPr_2NEt, THF.

Scheme IV. Preparation of Trifluoromethyl Alcohols and Ketones[a]

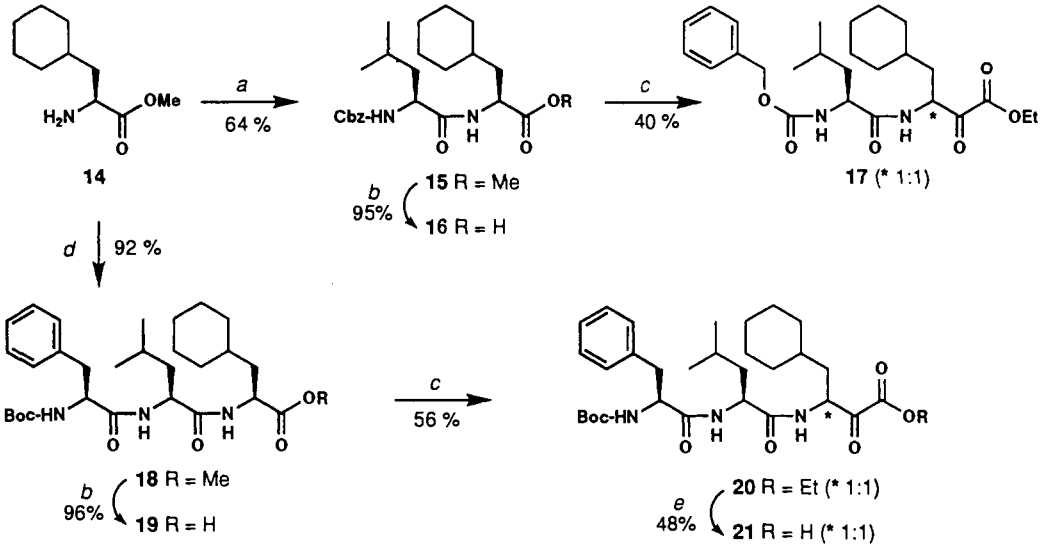


[a] Reagents: (a) LDA, $[CF_3CHO]$, THF, -20 °C; (b) 1. Et_3N, TBSOTf; 2. K_2CO_3; (c) Et_3N, DPPA, BnOH, hexane, reflux 14 h; (d) H_2, $PD(OH)_2/C$; (e) TBAF; (f) pTsOH; (g) Boc-Phe-Leu-OH **6**, DCC, HOBt, iPr_2NEt, THF; (h) Dess-Martin [O].

employed for the reaction, and if the enol anhydride formed during the course of the reaction was hydrolyzed by stirring with $NaHCO_3$/EtOH at room temperature rather than reflux temperature (56%). The dipeptidic α-keto ester **17** was synthesized in an analogous manner starting from **14**. Attempts were also made at synthesizing α-keto esters bearing histidine instead of leucine at the P_2 position via this route.[23] Mild hydrolysis of **20** provided the α-keto acid **21** in moderate yields (48%).

The encouraging biological data on the tripeptidic α-keto ester **20** (*vide infra*) prompted us to develop a chiral route for these molecules. While several retrosynthetic disconnections were envisioned and attempted,[24] only the most successful strategy is discussed below. An obvious advantage of this route is that it provides an easy access to the corresponding α-hydroxy esters, which can also be considered as transition-state analogs.[25] Condensation of the ester anion synthon tris(methylthio)methane[26] with the aldehyde **2** gave a diastereomeric mixture (4:1) of the α-hydroxy ortho thioesters **22** and **23** in 63% overall yield. Most of the major diastereomer **22** (34%) crystallized cleanly from the crude reaction mixture and chromatographic purification of the rest of the material gave a further 16% of **22** and 13% of the minor, slow-moving diastereomer **23**. Mercury-catalyzed hydrolysis[27] of diastereomers **22** and **23** afforded the corresponding α-hydroxy esters **24** and **25**, respectively. At this stage, stereochemical correlations were made in the following manner.[28] The two diastereomers were individually deprotected with 1:1 TFA/CH_2Cl_2 and the amine salts coupled with CDI to yield the cyclic carbamates **26** and **27**. In the ^1H NMR, the H_1 proton of *cis* oxazolidinone is expected to appear downfield and have a larger coupling constant when compared to the *trans* isomer.[29] A remote substituent effect in ^{13}C NMR is the steric compression effect wherein sterically perturbed carbon atoms are expected to appear at higher field than similar carbons that are not crowded.[30] The spectral data summarized in Scheme VI led to the unambiguous assignment of *trans* and *cis* stereochemistry for oxazolidinones **26** and **27**, respectively. This in turn translated to *anti* stereochemistry for the major diastereomer **22** and *syn* for the minor isomer **23**. It was gratifying to realize that for peptidic α-hydroxy esters, superior potency was demonstrated by the *trans* diastereomers derived from the major isomer **22** (*vide infra*).

Scheme V. Preparation of α-Keto Esters via Modified Dakin-West Reaction[a]



[a] Reagents: (a) Cbz-Leu-OH, DCC, HOBt, iPr_2NEt; (b) 1 N NaOH, MeOH; (c) EtOC(O)C(O)Cl, pyridine, DMAP, THF/DMF (1:1), reflux, 2 h; (d) Boc-Phe-Leu-OH **6**, DCC, HOBt, iPr_2NEt, THF/DMF (1:1); (e) K_2CO_3, EtOH.

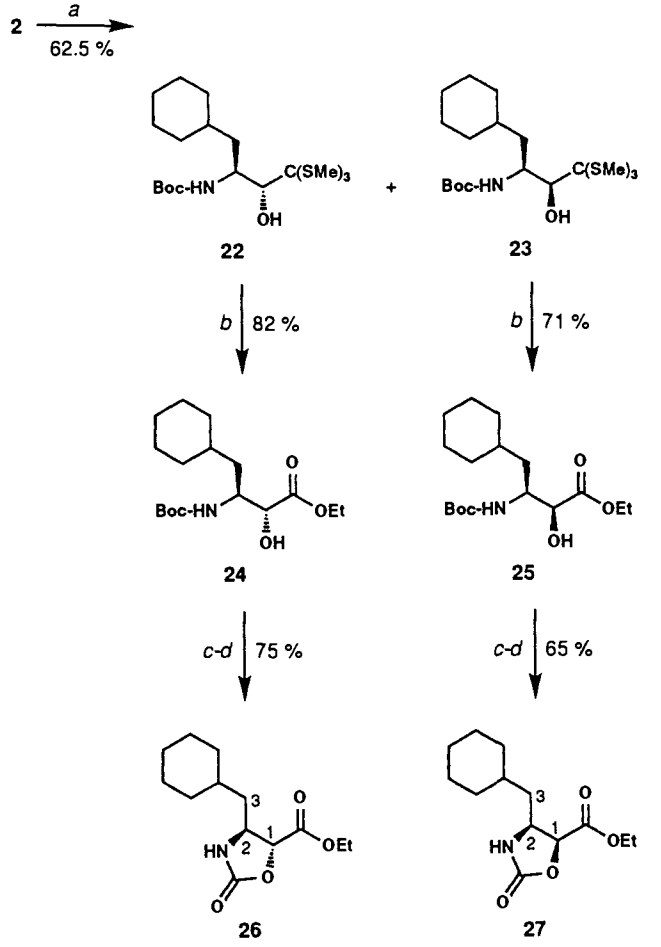
The *trans*-α-hydroxy ester **24** was deprotected and coupled with Boc-L-leucine to give **28** (Scheme VII). Coupling of the free amine derived after removal of the Boc group from **28** with the morpholino acid **29**[31] provided the *anti*-hydroxy ester **30**. Oxidation of tripeptide **30** with the Dess–Martin periodinane reagent proceeded smoothly to provide the chiral α-keto ester **31** in 90% yield. Thus, our objective of achieving a chiral synthesis was accomplished, but, unfortunately, we found that the α-keto ester **31** slowly epimerized on standing. Thus, a ^{13}C NMR of **31** run immediately after its synthesis showed it to be a single diastereomer, whereas a sample run after 1 week revealed a roughly 1:1 mixture of two diastereomers, thereby highlighting the relative susceptibility of peptidic α-keto esters toward epimerization.[32] The free amine of **24** was also coupled with the dipeptide acid **6** to provide the *trans* hydroxy ester tripeptide **32**. The corresponding *syn* diastereomer **33** was prepared in an analogous manner starting with the *erythro* intermediate **25**.

It was interesting to compare the hydrating ability of the two classes of compounds. Thus, while the trifluoromethyl ketone **13** was readily hydrated and was isolable only as a hydrate, the keto ester **31** existed mainly in the free ketone form. The ^{13}C NMR of **31** in CD_3OD initially showed only the ketone carbonyl (194 ppm) and the peak due to hemiketal formation (100 ppm) appeared gradually and intensified with time at the expense of the carbonyl peak (Scheme VIII). This suggested that the hemiketal formation was a slow equilibrium process in the case of the α-keto ester **31**.

Preparation of α-diketones. Compared to the fluoro ketones and α-keto esters, the α-diketones are a much less well-studied class of inhibitors.[33,34] To date, there has been only one specific report on the preparation of β-amino α-diketones, but it is restricted to the preparation of methyl diketones.[34] We adopted a strategy similar to the one utilized for α-keto esters for preparing this class of compounds, utilizing 1,3-dithiane as a formyl anion synthon.[35] If successful, this would constitute a versatile route for their preparation and enable access to a wide variety of peptidic diketones in a straightforward manner. An additional advantage of this route would be that the penultimate α-hydroxy ketone intermediates would also be available for evaluation as proteinase inhibitors. Thus, reaction of the lithio anion of 2-*n*-propyl-1,3-dithiane (**36**)[36] with aldehyde **2** gave the single diastereomer **37** in 35% yield (Scheme IX). Although a definitive assignment of the absolute stereochemistry of **37** cannot be made, on the basis of our own experience with related nucleophiles like ortho thioesters, the reaction was expected to favor the formation of the desired *anti* diastereomer.[37] This is further supported by the relative potency of the corresponding hydroxy ketones (*vide supra*, see the biological section). Removal of the Boc group with anhydrous HCl in ethyl acetate followed by coupling of the amine salt **38** with appropriate dipeptide acids **6** and **35** gave the tripeptides **39** and **40**, respectively. Oxidative cleavage of the dithiane group in **39** with ceric ammonium nitrate[38] furnished the hydroxy ketone **41** in 48% yield. Subsequently, we have realized that this deprotection can in general be accomplished very efficiently and cleanly when thallium nitrate[39] is employed as the oxidant. Thus, removal of the dithiane group from the tripeptide **40** with the latter reagent gave the desired α-hydroxy ketone **42** in 83% yield. The hydroxy ketones **41** and **42** were smoothly oxidized in high yields to α-diketones using Dess–Martin periodinane.[19]

Preparation of histidine-containing diketones required a judicious choice of complementary protecting groups for the imidazole ring of histidine and for the diketone moiety, and coupling procedures that would be tolerated by these protecting groups. Among several histidine-protecting groups that are available, the tosyl group appeared to be most compatible with our route for preparing α-diketones, i.e. the reaction conditions needed for regeneration of the diketone functionality from the hydroxy dithiane fragment. Since the tosyl group cannot survive the standard DCC/HOBt coupling conditions, Boc-*N*-tosylhistidine (**45**)[40] was coupled with **38** using triethylamine and diphenylphosphoryl azide yielding 71% of the desired product **46**[41] (Scheme X). A substantial amount (21%) of the deprotected compound **47** resulting from removal of the tosyl group was also obtained which fortunately could be easily reprotected using $TsCl/Et_3N$ to **46** in essentially quantitative yields. Treatment of **46** with thallium nitrate afforded the hydroxy ketone **48**,

Scheme VI. Preparation and Stereochemistry of α-Hydroxy Ester Intermediates[a]



^{1}H NMR:	H-1	4.55 ppm (J = 5.1 Hz)	5.04 ppm (J = 8.5 Hz)
^{13}C NMR:	C-1	78.3 ppm	76.7 ppm
	C-2	53.8 ppm	52.0 ppm
	C-3	43.6 ppm	38.0 ppm

[a] Reagents: (a) nBuLi, $HC(SMe)_3$; (b) $HgCl_2$, HgO, 95% aqueous EtOH; (c) TFA/CH_2Cl_2 (1:1); (d) CDI, NMM.

which after removal of the tosyl group with HOBt/MeOH[40b] furnished the histidine-containing dipeptidic α-hydroxy ketone **49**. On the other hand, oxidation of **48** followed by HOBt treatment of the intermediate diketone **50** afforded the histidine bearing 1,2-diketone **51**. As expected, both **49** and **51** were found to be water soluble. To our disappointment, the diketone **51** was found to be unstable to storage, and it was therefore not tested for renin inhibitory activity.

Biology

The I_{50} values of various activated ketones and their precursor alcohols against human renin are summarized in Table I.

Since alcohols can also be viewed as transition-state analogs, both the activated ketones and the corresponding alcohols were tested for inhibitory potency against human renin. The 1:1 diastereomeric mixture of the simple baseline alcohol **7** was only weakly active when tested against human renin (I_{50} = 3200 nM). In the tripeptide alcohol **12**, the methyl group of **7** is replaced by a trifluoromethyl group. This substitution increases the

Table I. *In Vitro* Activity of Various Classes of Renin Inhibitors[a]

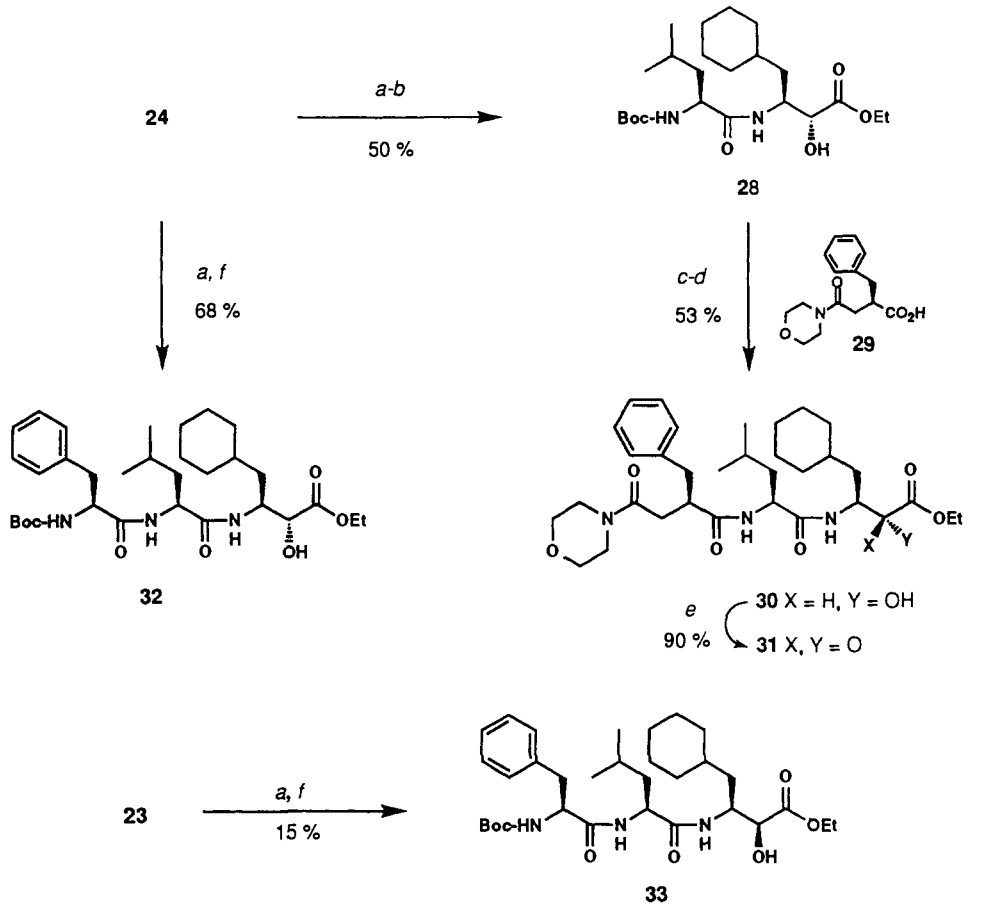
compd no.	I_{50} (nM, human renin)
	Baseline Compound
7	3200 ± 750 (2)
	Trifluoromethyl Alcohol and Ketone
12	4000 ± 750 (2)
13	250 ± 32 (3)
	α-Hydroxy Esters and Ketones
17	52 000 (1)
20[b]	15 ± 2 (4)[b]
21	64 000 (1)
30	4.7 ± 1.1 (3)
31	4.1 ± 0.3 (3)
32	5.3 ± 0.5 (3)
33	110 ± 19 (3)
	α-Hydroxy Ketones and Diketones
39	2200 ± 500 (2)
41	23 ± 2 (2)
42	14 ± 2 (3)
43	52 ± 7 (3)
44	28 ± 2 (2)
49	420 000 (1)

[a] See the general Experimental Section for a description of the method for determining the I_{50} values of these inhibitors. Number of determinations is indicated in parentheses. [b] Compound **20**: I_{50} (porcine pepsin) = 2700 nM; I_{50} (bovine cathepsin D) = 1300 nM.

acidity of the adjacent hydroxyl group by ca. 4 pKa units, thereby making it a better hydrogen atom donor. Additionally, the fluorine atoms are themselves capable of weak H-bond acceptor interactions. The nearly equal activity of **12** (I_{50} = 4000 nM) to **7** suggests that the beneficial effect from such binding contributions, if any, was minimal. The 1,1,1-trifluoromethyl ketone **13** (I_{50} = 250 nM), which existed completely in its hydrated form on the basis of ^{13}C NMR data (see Experimental Section), was about 10-fold more active than the corresponding alcohol **12**. This difference in activity demonstrates the importance of the hydrated carbonyl group in binding to the enzyme. After the completion of our work, a similar magnitude of activity difference was reported in the literature between various peptidic perfluoroalkyl alcohols and ketones as renin inhibitors.[42] A similar activity trend has also been observed with various difluorostatine alcohols and the corresponding difluorostatone-based renin inhibitors.[43-46] However, this is not a general rule since examples with minimal difference between the activity of fluoro alcohols and the corresponding ketones have also been reported.[48]

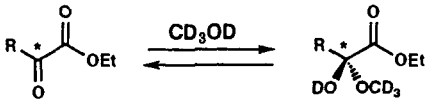
The inhibitory potency of α-hydroxy ester **32** (I_{50} = 5.3 nM) compares well with that of similar renin inhibitors reported in the literature.[25] The corresponding *syn* analog **33** was substantially less active (I_{50} = 110 nM), indicating the preference for *anti*, statine-like stereochemistry of the hydroxyl group for this class of renin inhibitors.[25,48] Interestingly enough, the α-hydroxy ester **32** was over 100-fold more active than the simple tripeptide alcohols **7** and **12**, suggesting a significant contribution toward binding from the ester group. Participation in productive H-bonding interactions by the ethyl ester moiety and/or hydrophobic interaction by its ethyl group at the S_1' subsite are the most likely explanations for this impressive 2 orders of magnitude enhancement in activity. This observation is in accordance with the concept of extended binding for renin inhibitors. In general, various tripeptide renin inhibitors have exhibited significant levels of improvement in activity when modified by introduction of groups capable of interacting at the S_1' subsite of the enzyme.[42-47] For example, while our trifluoromethyl alcohol **12** was only

Scheme VII. Preparation of α-Keto Esters via Oxidation of α-Hydroxy Esters[a]



[a] Reagents: (a) TFA/CH_2Cl_2 (1:1); (b) DCC, HOBt, iPr_2NEt, Boc-Leu-OH; (c) HCl/AcOH, EtOAc; (d) DCC, HOBt, iPr_2NEt, **29**; (e) Dess–Martin [O]; (f) DCC, HOBt, iPr_2NEt, Boc-Phe-Leu-OH **6**.

Scheme VIII. Hemiketal Formation of α-Keto Esters



^{13}C NMR: * 193.9 ppm * 100.1 ppm

Time (min)	A/B
15	only A
30	2.0
60	1.0
120	0.5
720	only B

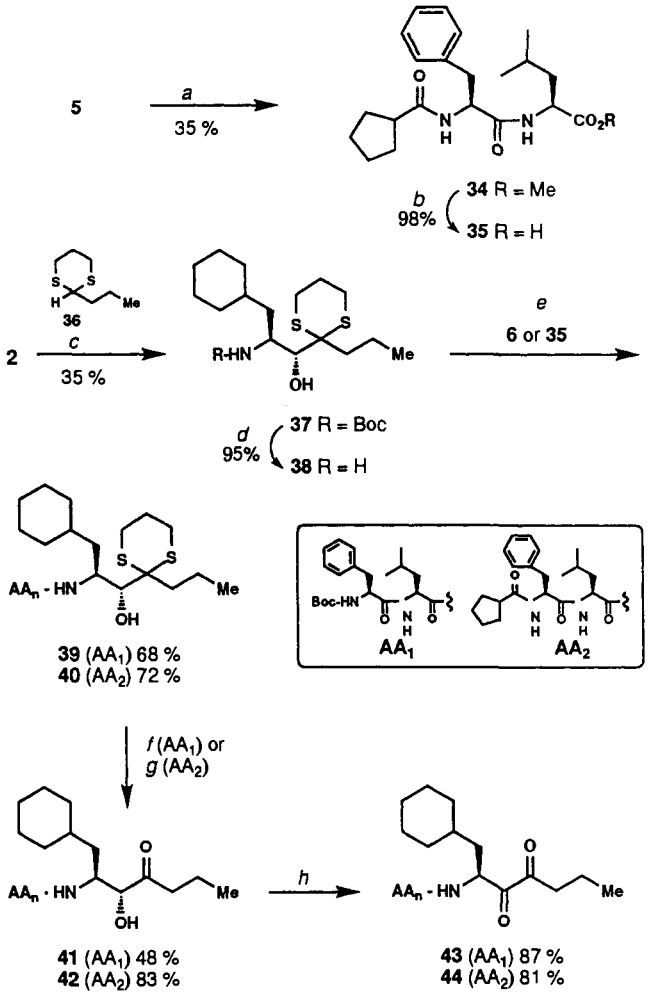
moderately active (I_{50} = 4000 nM), the structurally related perfluoropropyl alcohol has been reported to possess 75-fold better potency (I_{50} = 52 nM).[42] Similarly, a difluoro ketone bearing a retroamide bond and an isovaleryl side chain has also been found to be 70-fold more potent than the trifluoromethyl ketone **13**.[46] However, it is important to note that precise assay conditions, especially the pH, can also markedly influence the observed intrinsic activity of renin inhibitors.

Correcting for the diastereomeric contents, the α-keto ester **20** and the related analog **31** (I_{50} = 15 and 4.1 nM respectively), wherein the Boc-Phe group of **18** is replaced by a morpholino succinamide moiety, were essentially equipotent to their hydroxy analogs **32** and **30** (I_{50} = 5.3 and 4.7 nM, respectively). This contradicts the 10-fold superior activity observed by us and others for fluoro ketone based activated ketones in comparison to the corresponding fluoro alcohols. Additionally, compared to the trifluoromethyl ketone **13**, the keto esters **20** and **31** had 25-fold better potency. These results collectively suggest that contributions from H-bonding and/or hydrophobic binding interactions of an ethyl ester group are superior to that of a trifluoromethyl group (**32** and **30** vs **12** for alcohols, **20** and **31** vs **13** for ketones). Secondly, it is these interactions of the ethyl ester group that are more critical for the intrinsic activity of α-keto esters, rather than the ability of the ester group to activate and thereby hydrate the adjacent ketone functionality (**20** vs **32**, **31** vs **30**).

Truncation of the tripeptide moiety of α-keto ester **20** to the dipeptide analog **17** (I_{50} = 52 000 nM) proved to be detrimental toward potency, illustrating the requirement of a P_4–P_3 amide group for good binding. Not unexpectedly, the α-keto acid **21** (I_{50} = 64 000 nM) was more than 3 orders of magnitude weaker in potency than the corresponding ethyl ester **20**, highlighting the incompatibility of a negatively charged carboxylic acid function in close proximity with the two catalytic aspartic acid residues residing at the active site of the enzyme. The keto ester **20** showed a very high level of specificity toward human renin. For example, its I_{50} values against the aspartic proteinases pepsin and cathepsin D were 2700 and 1300 nM, respectively, making it roughly 2 orders of magnitude more selective for the targeted enzyme, renin.

The α-diketones are a relatively much less well-studied class of inhibitors.[33] After the completion of our own work,

Scheme IX. Preparation of α-Hydroxy Ketones and α-Diketones[a]



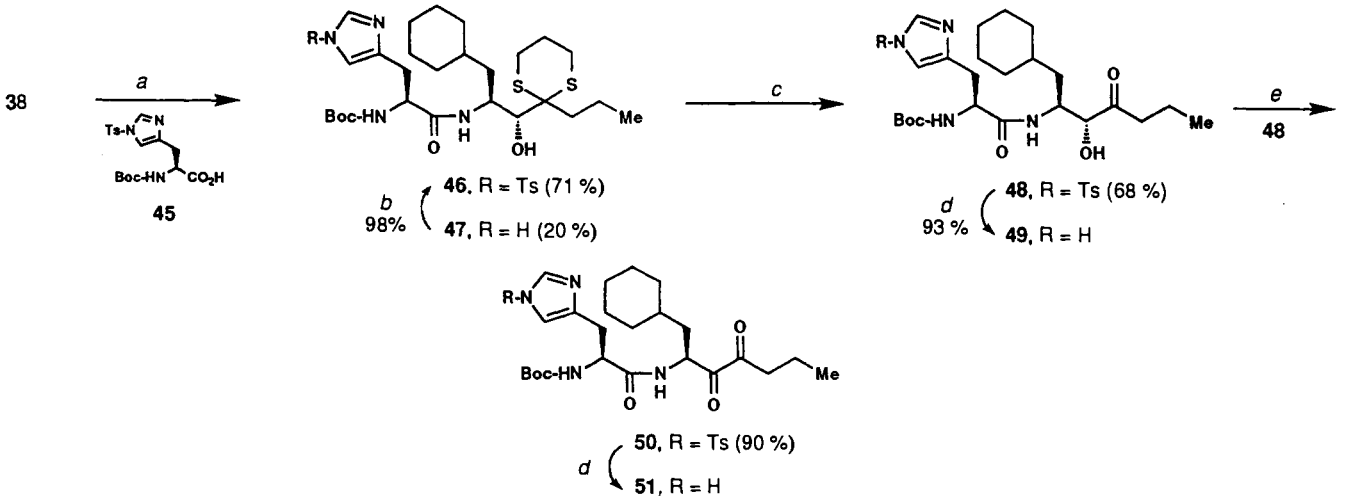
[a] Reagents: (a) (i) HCl, AcOH; (ii) DCC, HOBt, iPr_2NEt, C_5H_9-CO_2H; (b) NaOH, MeOH; (c) nBuLi, **36**; (d) anhydrous HCl, EtOAc; (e) DCC, HOBt, iPr_2NEt, **6** or **35**; (f) $Ce(NH_4)_2(NO_3)_6$; (g) $Tl(NO_3)_3 \cdot 3H_2O$, 3:1 MeOH/H_2O; (h) Dess–Martin [O].

their application as inhibitors of cysteine and serine proteinases was recently reported in the literature.[48] The tripeptidic α-diketones **43** and **44** (I_{50} = 52 and 28 nM, respectively) exhibited nanomolar levels of activity when evaluated for inhibition of human renin. Unlike the α-keto esters, the α-diketones did not epimerize and retained their chirality upon storage. While we did not evaluate the hydrating ability of this class of compounds, NMR studies in D_2O on related compounds reported in the literature suggest that one of the carbonyl groups is indeed hydrated.[48] The inhibitory potency of corresponding α-hydroxy ketones **41** and **42** (I_{50} = 23 and 14 nM, respectively) was actually 2-fold better than the corresponding diketones **43** and **44**, once again highlighting the predominance of binding interactions associated with the acyl group, as was observed for the α-hydroxy and keto–ester class of compounds. An attempt to truncate the size of these inhibitors was unsuccessful, as evidenced by the poor activity of dipeptidic α-hydroxy ketone **49** (I_{50} = 420 000 nM). Not unexpectedly, the dithiane intermediate **39** (I_{50} = 2 200 nM) of analogs **41** and **42** displayed inferior potency, highlighting the important contribution of the free carbonyl group and/or the poor fit of the bulky dithiane residue to that region of the enzyme.

Summary

The synthesis and biological evaluation of three different classes, namely the 1,1,1-trifluoromethyl ketones, α-keto esters, and α-diketone type of activated ketone based tripeptides as novel and potent (I_{50} = 4–250 nM) renin inhibitors is reported. In each series, the corresponding alcohols were also evaluated for their ability to inhibit human renin. The hydrating capability of the activated ketone functionality was important for intrinsic potency in the case of trifluoromethyl ketones, as illustrated by the 10-fold better activity of trifluoromethyl ketone analog **13** compared to its alcohol **12**. It was however unimportant for the α-keto ester (**20**, **31**) and α-diketone (**43**, **44**) based renin inhibitors, since they were found to be essentially equipotent to their corresponding alcohols (**32**, **30** and **41**, **42**, respectively). This suggests that potential side chain hydrophobic and/or H-bonding interactions of the adjacent ester or acyl group was more critical for *in vitro* activity than its ability to deactivate and thereby hydrate the neighboring ketone functionality. The general synthetic method developed for preparing peptidic α-diketones should facilitate the application of this relatively less well-studied class of activated ketones as novel inhibitors of various proteolytic enzymes.

Scheme X. Preparation of Histidine-Bearing α-Diketones[a]



[a] Reagents: (a) Et_3N, DPPA, CH_2Cl_2; (b) Et_3N, TsCl; (c) $Tl(NO_3)_3 \cdot 3H_2O$; (d) HOBt, MeOH; (e) Dess–Martin [O].

Experimental Section

General. All reactions were carried out under a positive pressure of dry argon, unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium or potassium/benzophenone ketyl prior to use. Acetonitrile, benzene, dichloromethane, diisopropylamine, hexane, methanol, pyridine, and toluene were distilled from calcium hydride prior to use.

TLC was performed using EM Science (E. Merck) 5- × 10-cm plates precoated with silica gel 60 F_{254} (0.25 mm thickness), and the spots were visualized by any of the following: UV, iodine, phosphomolymdic acid (PMA), ceric ammonium sulfate, anisaldehyde, vanillin, or Rydons stain. EM Science's silica gel 60 (230–400 mesh ASTM) was used for flash chromatography. A ratio of 25–100:1 silica gel/crude product by weight and a nitrogen pressure of 5–25 psi was normally employed for flash columns. Reverse-phase chromatographic purification of final compounds was carried out using CHP20P gel, a 75–150 μm polystyrene-divinyl benzene copolymer purchased from Mitsubishi Chemical Industries. Analytical HPLC was performed using two Shimadzu LC-6A pumps with an SCL-6B system controller and a C-R4AX chromatopac, and an SPD-6AV UV-VIS spectrophotometric detector. HPLC columns were commercially available from either Whatman or YMC Corporation.

Melting points were determined on an electrothermal Thomas Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on one of the following instruments: JOEL GX-400 operating at 400 (^{1}H) or 100 MHz (^{13}C), JOEL FX-270 operating at 270 (^{1}H) or 67.8 (^{13}C) MHz, and JOEL FX-60Q operating at 15 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and coupling constants (J) are in hertz (Hz). ^{19}F NMR spectra were recorded on a JEOL FX-90Q using $CFCl_3$ (δ = 0 ppm) as an external reference. IR spectra were recorded on a Mattson Sirius 100 FT-IR spectrophotometer, and the absorption maxima are reported in cm^{-1}. Mass spectra were recorded on a Finnigan MAT TSQ-4600 mass spectrometer (chemical ionization, CI) or a VG-ZAB-2F mass spectrometer (fast-atom bombardment, FAB). High-resolution mass spectra (HRMS) were determined using peak matching techniques versus PEG standards on a VG-ZAB-2F spectrometer. Optical rotations were measured using a Perkin-Elmer model 241 polarimeter and a 10-cm path length optical cell. Microanalysis results were adjusted to obtain the best fit assuming nonstoichiometric hydration.

***In Vitro* Inhibition Studies.** The human kidney renin used for assay of inhibitor potency was a partially purified preparation (no. 216, 2.4 μg AI/h/mg) generously provided by Dr. E. Haas (Mt. Sinai Medical Center, Cleveland, OH). The source of angiotensinogen substrate in renin incubation mixtures was human plasma (Mercer Regional Blood Center, Trenton, NJ). Incubation mixtures of 0.5 mL were buffered with 0.2 M TES, pH 7.0, and contained 0.10 mM EDTA, 0.10 mM sodium tetrathionate, and 0.04 mM phenylmethanesulfonyl fluoride. Renin concentrations in the mixtures were adjusted to generate angiotensin I (AI) at rates, constant with time, of 20–80 ng AI/mL/h. Human plasma was added at concentrations (10–50%) sufficient to provide a final angiotensinogen concentration of 0.5 μM. Inhibition test compounds were dissolved, serially diluted, and added to incubation mixtures in dimethyl sulfoxide (DMSO), with the final DMSO concentration fixed at either 0.5% or 1.0%. Incubations were conducted for 30 min at 37 °C. After the reactions were terminated by reduction of the temperature to 0 °C, AI concentrations were measured by radioimmunoassay. Inhibitor potencies were expressed as I_{50} values, the interpolated concentrations corresponding to 50% inhibition of renin activity. For the 13 compounds demonstrating I_{50} concentrations below 10 000 nM, I_{50} concentrations are mean values determined from 2–4 experiments; standard errors for the mean I_{50} concentrations ranged from 7% to 23%.

Inhibition of the activities of porcine pepsin (Sigma Chemical Co., St. Louis, MO) and bovine cathepsin D (Sigma) were measured in assays based upon the hydrolysis of 1.6% bovine hemoglobin (Sigma) at pH 1.6 (0.05 M HCl) and pH 3.5 (0.2 M sodium formate buffer), respectively. After incubation periods of up to 75 min at 37 °C, protein in the incubation mixtures was precipitated with 3.1% trichloroacetic acid (final concentration), and concentrations of peptidic products in the supernatant fractions were measured by rates of increase in absorbance at 280 nm to determine protease activity. Test compound was dissolved and diluted in DMSO and added to incubation mixtures at final DMSO concentrations of 2.0% or lower. Inhibitory potencies were expressed as I_{50} concentrations. Pepstatin A, employed as a standard aspartyl protease inhibitor in these assays, displayed an I_{50} concentration of <5 nM against both pepsin and cathepsin D.

(*S*)-α-[[(1,1-Dimethylethoxy)carbonyl]amino]-*N*-methoxy-*N*-methylcyclohexanepropanamide (1).[10] 1,1′-Carbonyldiimidazole (CDI, 9.95 g, 61.1 mmol) was added over 10 min to an efficiently stirring solution of Boc-L-cyclohexylalanine (13.9 g, 51.2 mmol) in THF (150 mL) at 0 °C. After 30 min of stirring, *N*,*O*-dimethylhydroxylamine hydrochloride (5.49 g, 56.3 mmol) was added followed by triethylamine (7.9 mL, 56.3 mmol). After stirring at room temperature for 2.5 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The amber-colored residue was dissolved in Et_2O and poured into 1 N HCl (1000 mL). The two layers were separated, and the aqueous solution was further extracted with Et_2O. The combined ethereal extracts were washed sequentially with H_2O, saturated aqueous $NaHCO_3$, and saturated NaCl. Drying ($MgSO_4$) and concentration *in vacuo* gave 1 (16.1 g, 99%) as a colorless oil. TLC: R_f = 0.58 (1:1 hexane/ethyl acetate). MS: $(M + H)^+$ 315. $[\alpha]_D$ = −12.9° (c = 1.0, MeOH). ^{1}H NMR ($CDCl_3$): (s, 0.8–2.1 (m, 13 H), 1.44 (s, 9 H), 3.20 (s, 3 H), 3.78 (s, 3 H), 4.75 (m, 1 H), 5.06 (d, 1 H, J = 9.4). ^{13}C NMR ($CDCl_3$): 26.0, 26.2, 26.4, 28.3, 32.2, 34.0, 40.4, 48.3, 61.4, 79.6, 155.6, 173.9. Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.11; H, 9.62; N, 8.91. Found: C, 61.35; H, 9.54; N, 9.10.

(*S*)-α-[[(1,1-Dimethylethoxy)carbonyl]amino]cyclohexanepropanal (2). A 1 M THF solution of $LiAlH_4$ (Aldrich, 85.4 mL, 85.4 mmol) was added dropwise over a period of 20 min to a solution of the Weinreb amide 1 (17.88 g, 56.94 mmol) in 350 mL of ether at 0 °C (caution, exothermic!). After an additional 30 min at 0–2 °C, the reaction mixture was quenched with 250 mL of 5% $KHSO_4$ (caution, exothermic!) and warmed to room temperature, and the aqueous and organic layers were separated. The aqueous layer was diluted with 250 mL of H_2O and reextracted with ether (2 × 150 mL). The combined organic extracts were washed sequentially with 5% HCl (1 × 150 mL), saturated aqueous $NaHCO_3$ (1 × 150 mL) and saturated aqueous NaCl (2 × 150 mL). After the extracts were dried over Na_2SO_4, the ethereal solution was filtered through Celite and concentrated *in vacuo* to give 12.56 g (85.8%) residue which looked homogeneous by TLC, R_f = 0.53 (1:1 hexane/ethyl acetate). $[\alpha]_D$ = −37.2° (c = 5.6, CH_3OH). IR: 3075, 3050, 695. ^{13}C NMR ($CDCl_3$): 25.9, 26.0, 26.2, 28.2, 32.5, 33.7, 36.6, 57.7, 79.9, 155.5, 200.4.

(β*S*)-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-methylcyclohexanepropanol (3). Methyl magnesium bromide (3.0 M, 17.9 mL, 53.7 mmol) was added to a solution of **2** (4.57 g, 17.9 mmol) in THF (90 mL) at −78 °C. After stirring for 5 min at −78 °C, the reaction mixture was warmed to 0 °C and then stirred overnight with gradual warming to room temperature. After 16 h, the reaction was quenched with saturated aqueous NH_4Cl (90 mL) and THF was removed *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water H_2O (75 mL), and the aqueous layer was reextracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated. Chromatographic purification of the crude product (4.4 g, 4:1 hexane/ethyl acetate) yielded 2.87 g (60%) of **3**. TLC: R_f = 0.53 (1:1 hexane/ethyl acetate). MS: $(M + H)^+$ 272. $[\alpha]_D$ = −25.5° (c = 1.32, MeOH). ^{1}H NMR ($CDCl_3$): 1.2 (d, 3 H, J = 6), 0.7–2.5 (m, 13 H), 1.45 (s, 9 H), 3.45–3.95 (m, 2 H), 4.45–4.7 (m, 1 H). ^{13}C NMR ($CDCl_3$): 20.1, 26.0, 26.2, 26.4, 27.9, 28.2, 32.3, 32.6, 33.8, 34.1, 37.2, 39.8, 52.9, 53.3, 69.4, 70.5, 78.8, 79.2, 156.4, 156.5. Anal. Calcd for $C_{15}H_{29}N_1O_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.63; H, 10.58; N, 5.20.

(β*S*)-β-Amino-α-methylcyclohexanepropanol (4). **3** (1.71 g, 6.3 mmol) was dissolved in a solution of ethyl acetate saturated with anhydrous HCl (app 1.5 M, 30 mL) and stirred for 1 h at room temperature. Concentration followed by trituration of the residue with hexane gave 1.4 g of solid hydrochloride salt, which was directly employed for subsequent reactions. MS (CI, +/-

ions): $(M + H)^+$ 172 , $(M + Cl)^-$ 206. Anal. Calcd for $C_{10}H_{22}NClO \cdot 0.27H_2O$: C, 56.48; H, 10.69; N, 6.59; Cl, 16.67. Found: C, 56.68; H, 10.41; N, 6.42; Cl, 16.40.

***N*-[*N*-[(1,1-Dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucine, Methyl Ester (5).** DCC (10.315 g, 50 mmol) was added to a solution of Boc-L-phenylalanine (13.265 g, 50 mmol), L-leucine methyl ester (9.085 g, 50 mmol), HOBT (7.65 g, 50 mmol), and iPr_2NEt (8.7 mL, 50 mmol) in THF (150 mL) at 0 °C, and the reaction was left for overnight stirring with gradual warming to room temperature. The next day (total reaction time, 14 h), the precipitated urea was filtered off and the filtrate concentrated *in vacuo*. The residue was taken up in EtOAc (500 mL) and washed sequentially with saturated aqeuous $NaHCO_3$ (2 × 200 mL) and saturated aqueous NaCl (1 × 100 mL), dried (Na_2SO_4), and concentrated to give a crude solid. Crystallization from ethyl ether gave pure 5 (11.61 g). Concentration of the mother liquor followed by chromatographic purification of the residue eluting with 4:1 hexane/ethyl acetate gave additional 5 (1.35 g, total 12.96 g, 66.1%). TLC: R_f = 0.57 (1:1 hexane/ethyl acetate). Mp: 104–105 °C. MS: $(M + H)^+$ 393. $[\alpha]_D$ = −17.5° (*c* = 1.2, MeOH). ^1H NMR ($CDCl_3$): 0.9 (m, 6 H), 1.15–1.7 (m, 3 H), 1.42 (s, 9 H), 3.08 (d, 2 H, *J* = 7), 3.7 (s, 3 H), 4.35 (m, 1 H), 4.58 (m, 1 H), 5.0 (br s, 1 H), 6.3 (d, 1 H, *J* = 7), 7.1–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 21.9, 22.7, 24.6, 28.2, 38.1, 41.6, 50.7, 52.2, 55.0, 80.2, 126.9, 128.6, 129.3, 136.6, 155.3, 170.9, 172.8. Anal. Calcd for $C_{21}H_{32}N_2O_5$: C, 64.3; H, 8.15; N, 7.14. Found: C, 64.12; H, 8.16; N, 7.02.

***N*-[*N*-[(1,1-Dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucine (6).** NaOH (1 N, mL, 6 mmol) was added to a solution of Boc-Phe-Leu-OMe prepared above (1.92 g, 5 mmol) in methanol (20 mL). After 1 h, the solution was concentrated and the residue was suspended in EtOAc (50 mL) and H_2O (20 mL). While stirring, the biphasic solution was acidified to pH 3.5 with concentrated HCl and the two layers were separated. The aqueous solution was reextracted with EtOAc (2 × 50 mL). The combined organic extracts were dried and concentrated to give a residue which after trituration with ethyl ether gave 6 (1.87 g, 99%). Mp: 143–146 °C. TLC: R_f = 0.4 (9:1:0.1 $CHCl_3$/MeOH/AcOH). MS: $(M + H)^+$ 379. $[\alpha]_D$ = −13.98° (*c* = 1.48, MeOH). IR (KBr): 3327, 2959, 1728, 1670, 1534, 1173, 698. ^1H NMR (CD_3OD): 0.93 (d, 3 H, *J* = 7), 0.95 (d, 3 H, *J* = 7), 1.35 (s, 9 H), 1.5–1.8 (m, 3 H), 2.79 (dd, 1 H, *J* = 9.4, 13.7), 3.12 (dd, 1 H, *J* = 4.7, 13.7), 4.33 (q, 1 H, *J* = 5.1, 9.4), 4.45 (t, 1 H, *J* = 7.3), 7.25 (s, 5 H). ^{13}C NMR (CD_3OD): 21.9, 23.4, 25.8, 28.6, 39.0, 41.8, 52.0, 57.1, 80.5, 127.6, 129.3, 130.4, 157.3, 174.3, 175.7. Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.31; H, 7.78; N, 7.37.

***N*-[1-(Cyclohexylmethyl)-2-hydroxypropyl]-N^2-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (7).** The hydrochloride salt 4 (414 mg, 2 mmol) was added to a solution of BOC-Phe-Leu-OH 6 (756 mg, 2 mmol) in THF (8 mL) and cooled to 0 °C. HOBt (306 mg, 2 mmol), iPr_2NEt (383 μL, 2.2 mmol) and DCC (412.6 mg, 2 mmol) were added sequentially, and the reaction was stirred overnight with gradual warming to room temperature. After 16 h at room temperature, the reaction mixture was concentrated and the residue was treated with CH_2Cl_2 and filtered. The organic filtrate was washed sequentially with 10% citric acid (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and saturated aqueous NaCl (10 mL). Drying and concentration gave 0.95 g of crude product which was purified by flash chromatography (1:1 hexane/ether to 1:1 hexane/ethyl acetate) to afford 514.8 mg (48.5%) of 7. Mp: 145–147 °C. MS (CI, +/- ions): $(M + H)^+$ 532, $(M + Cl)^-$ 566 , M − Cl)⁻ 530. TLC: R_f = 0.42 (90/10/1/0.1 $CHCl_3$/MeOH/H_2O/AcOH). $[\alpha]_D$ = −37.8° (*c* = 1.26, MeOH). ^1H ($CDCl_3$): 0.92 (d, 6 H, *J* = 6), 1.12 and 1.2 (d, 3 H, *J* = 6), 0.75 - 1.85 (m, 16 H), 1.42 (s, 9 H), 3.0–3.17 (m, 2 H), 3.65–4.05 (m, 2 H), 4.25–4.4 (m, 2 H), 4.95 (m, 1 H), 6.38 (m, 2 H), 7.15–7.35 (m, 5 H). ^{13}C ($CDCl_3$): 18.4, 20.0, 22.2, 22.5, 24.5, 25.9, 26.0, 26.1, 26.3, 28.0, 32.3, 32.8, 33.5, 33.8, 34.1, 36.3, 37.9, 38.8, 40.9, 41.2, 52.0, 52.2, 52.6, 55.4, 68.6, 70.3, 79.8, 126.5, 128.2, 129.1, 130.7, 136.4, 155.5, 171.7, 172.1. Anal. Calcd for $C_{30}H_{49}N_3O_5 \cdot 0.24H_2O$: C, 67.22; H, 9.30; N, 7.84. Found: C, 67.34; H, 9.20; N, 7.78.

α-(2,2,2-Trifluoro-1-hydroxyethyl)cyclohexanepropanoic Acid (8). nBuLi (2.5 M, 152.68 mL, 382 mmol) was added dropwise to a solution of iPr_2NH (53.5 mL, 382 mmol) in THF (250 mL) at −78 °C. After sirring for 5 min at −78 °C and 30 min at −10 °C to ensure complete formation of LDA, a solution of cyclohexane propionic acid (30 mL, 173.5 mmol) in THF (30 mL) was added, and stirring was continued for 1 h at −10 °C. The reaction was then cooled to −50 °C and freshly generated trifluoroacetaldehyde was cannulated into the reaction flask. [Trifluoroacetaldehyde was prepared by refluxing a 100-g 1:1 mixture of trifluoroacetaldehyde ethyl hemiacetal and concentrated sulfuric acid and condensing the liberated gaseous product in a side arm flask precooled to −78 °C[16]. After stirring for 2 h with gradual warming to room temperature, the reaction was quenched with water (10 mL), concentrated to remove THF, and partitioned between EtOAc (250 ml) and 10% HCl (350 mL). The aqueous layer was reextracted with EtOAc (3 × 250 mL), and the combined organic extracts were washed with saturated aqueous NaCl (1 × 200 mL). Drying (Na_2SO_4) and concentration afforded 66.6 g of crude product. Purification by flash chromatography (30:1:0.1 to 19:1:0.1 $CHCl_3$/MeOH/AcOH) followed by trituration with toluene to remove traces of acetic acid, afforded 29.26 g (66.7%) of pure 8. MS: $(M + H)^+$ 255, $(M - H)^-$ 253. TLC: R_f = 0.4 (9:1:0.1 $CHCl_3$/MeOH/AcOH). ^1H ($CDCl_3$): 0.75–2.0 (m, 13 H), 2.6–2.87 (m, 1 H), 3.95–4.15 (m, 1 H), 4.97 (br S, 1 H). ^{13}C (CD_3OD): 27.2, 27.3, 27.4, 27.6, 33.2, 33.6, 34.9, 35.5, 36.7, 37.0, 38.3, 44.8, 45.6, 71.8, 72.3, 72.7, 126.6 (q, *J* = 283), 175.6, 177.1.

α-[1-[[(1,1-Dimethylethyl)dimethysilyl]oxy]-2,2,2-trifluoroethyl]cyclohexanepropanoic Acid (9). TBDMS-OTf (73.8 mL, 321 mmol) was added dropwise to a solution of 8 (27.17 g, 107 mmol) and Et_3N (44.7 mL, 321 mmol) in CH_2Cl_2 (430 mL) at 0 °C. After overnight stirring with gradual warming to room temperature, the reaction was quenched with H_2O (500 mL) and extracted with additional CH_2Cl_2 (3 × 350 mL). The combined organic extracts were concentrated, and the crude disilylated product was stirred with K_2CO_3 (1 M, 340 mL) in MeOH (500 mL) for 1.5 h at room temperature. MeOH was removed *in vacuo*, and the aqueous solution was acidified in the presence of EtOAc (600 mL) to pH = 5.3 using 10% aqueous HCl. The two layers were separated, and the aqueous layer was reextracted with EtOAc (3 × 250 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the crude product was flash chromatographed (2:1 hexane/EtOAc) to afford 38.6 g (98%) of pure 9. TLC: R_f = 0.62 (1:1 hexane/ethyl acetate). MS: $(M + H)^+$ 369, $(M - H)^-$ 367, $(2M - H)^-$ 735. ^1H ($CDCl_3$): 0.1 (s, 6 H), 0.65–1.9 (m, 22 H), 2.7–2.92 (m, 1 H), 4.05–4.4 (m, 1 H), 9.05 (br S, 1 H). ^{13}C (CD_3OD): −4.5, −4.8, 19.0, 26.2, 27.0, 27.3, 27.6, 33.2, 35.4, 35.6, 36.7, 45.2, 73.5 (q, *J* = 30.3), 126.0 (q, *J* = 284), 176.2. Anal. Calcd for $C_{17}H_{31}O_3F_3Si$: C, 55.41; H, 8.48; F, 15.46. Found: C, 55.25; H, 8.55; F, 15.25.

[1-(Cyclohexylmethyl)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,3,3-trifluoropropyl]carbamic Acid, Phenylmethyl Ester (10). Diphenylphosphoryl azide (DPPA 1.243 mL, 5.775 mmol) was added to a premixed and vigorously stirring solution of 9 (1.93 g, 5.25 mmol) and Et_3N (0.768 mL, 5.512 mmol) in hexane (21 mL). After 3 h reflux, complete disappearance of the acyl azide intermediate (2150 cm^{-1}) and formation of the rearranged isocyanate (2250 cm^{-1}) was revealed by IR. At this stage, benzyl alcohol (0.598 mL, 5.775 mmol) and additional Et_3N (0.768 mL, 5.512 mmol) were added, and the reaction mixture was vigorously stirred and refluxed for an additional 18 h. It was then taken up in EtOAc (50 mL) and washed sequentially with H_2O (1 × 25 mL), saturated aqueous $NaHCO_3$ (1 × 25 mL), 1% aqueous HCl (1 × 25 mL), and saturated NaCl (1 × 25 mL). Drying (Na_2SO_4) and concentration gave 2.448 g of crude product, which was purified by flash chromatography (9:1 hexane/Et_2O) to give 1.837 g (75%) pure 10. The reaction was repeated on a 50 mmol scale to provide 15.76 g (66.7%) 10. TLC: R_f = 0.43 (4:1 hexane/Et_2O). MS: $(M + H)^+$ 474, $(M - H)^-$ 472. ^1H NMR ($CDCl_3$): 0.1 (s, 3 H), 0.17 (s, 3 H), 0.9 and 0.95 (2s, 9 H), 0.7–1.9 (m, 13 H), 3.8–4.27 (m, 2 H), 4.6 and 4.9 (2d, 1 H, *J* = 8), 5.13 (m, 2 H), 7.35 (m, 5H) ^{13}C NMR ($CDCl_3$) : −5.3, −5.1, −4.9, 18.1, 25.6, 25.9, 26.1, 26.2, 26.3, 26.4, 31.8, 32.6, 33.6, 33.8, 34.0, 34.4, 35.4, 39.5, 48.6, 49.3, 66.7, 66.8, 71.9 (q, *J* = 28.4), 73.0 (q, *J* = 28.4), 124.3 (q, *J* = 282), 127.9, 128.0, 128.2, 128.5, 136.3, 136.5, 155.5, 155.7. Anal. Calcd for $C_{24}H_{38}NO_3F_3Si$: C, 60.86; H, 8.09; N, 2.96; F, 12.03. Found: C, 60.85; H, 7.97; N, 3.11; F, 11.96.

β-Amino-α-(trifluoromethyl)cyclohexanepropanol, 4-Methylphenyl) Sulfonate Salt (11). $Pd(OH)_2/C$ (Pearlman's catalyst, 3.6 g) was added to a solution of **10** (5.728 g, 12.1 mmol) in EtOAc (48 mL). After stirring under an atmosphere of hydrogen (balloon) for 20 h, the reaction mixture was filtered through Celite and the catalyst was washed with additional EtOAc. The combined filtrate was concentrated to give 3.43 g of the crude amine which was dissolved in THF (40 mL) and treated with $nBu_4N^+F^-$ (1 M in THF, 12.1 mL, 12.1 mmol). After 1 h, additional $nBu_4N^+F^-$ (1 M in THF, 6 mL, 6 mmol) was added to drive the reaction to completion. After 20 min, the reaction was judged to be complete by TLC. Concentration *in vacuo* gave a residue which was dissolved in EtOAc (300 mL) and washed sequentially with H_2O (1 × 150 mL), saturated Na_2CO_3 (2 × 150 mL), and saturated aqueous NaCl (1 × 150 mL). Drying (Na_2SO_4) and concentration gave the free amino alcohol **11** as a white solid (2.13 g, 10.24 mmol) which looked clean by TLC , R_f = 0.27 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). It was dissolved in MeOH (100 mL) and treated with pTsOH (1.9 g, 10.24 mmol). After stirring for 5 min, the tosylate salt of **11** precipitated out which was filtered to provide 2.84 g of the product. The mother liquor was concentrated, the residue suspended in Et_2O, and filtered to provide an additional 1.18 g of **11** (overall 83.7% yield from **10**). MS: $(M + H)^+$ 474, $(M - H)^-$ 472. ^1H NMR (CD_3OD): 0.65–1.9 (m, 13 H), 2.33 (s, 3 H), 3.42–3.65 (m, 1 H), 4.13 and 4.35 (dd, 1 H, J = 2, 8), 7.22 (d, 2 H, J = 9), 7.7 (d, 2 H, J = 9). ^{13}C NMR (CD_3OD): 21.3, 26.7, 26.8, 26.9, 27.1, 27.3, 32.9, 33.8, 34.1, 34.4, 35.0, 35.5, 38.8, 50.4, 69.0 (q, J = 32), 70.2 (q, J = 30), 125.7 (q, J = 282), 126.9, 129.8, 141.7, 143.4. Anal. Calcd for $C_{17}H_{26}NO_4F_3S$: C, 51.37; H, 6.59; N, 3.53; F, 14.34; S, 8.07. Found: C, 51.38; H, 6.62; N, 3.51; F, 14.49; S, 8.17.

***N*-[1-(Cyclohexylmethyl)-3,3,3-trifluoro-2-hydroxypropyl]-*N*²-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide** (12). HOBt (1.09 g, 7.15 mmol) and iPr_2NEt (1.36 mL, 7.865 mmol) were sequentially added to a solution of **6** (2.7 g, 7.15 mmol) and **11** (2.84 g, 7.15 mmol) in DMF (35 mL) at 0°. DCC (1.47 g, 7.15 mmol) was added after 5 min, and the reaction was left for overnight stirring with gradual warming to room temperature. After 12 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in EtOAc (250 mL) and washed sequentially with H_2O (2 × 150 mL), saturated aqueous $NaHCO_3$ (1 × 150 mL), 5% aqueous HCl (1 × 100 mL), and saturated NaCl (1 × 100 mL). Drying (Na_2SO_4) and concentration gave 4.35 g of crude product which was purified by flash chromatography (2:1 hexane/EtOAc) to give 3.12 g (75%) pure **12**. Mp: 123–126 °C. HPLC: t_R = 22.82 (18.4%), 23.12 (12.3%), 24.4 (33.3%), and 26.6 min (33.5%); 50–90% aqueous CH_3CN 50-min gradient, flow rate = 1 mL/min; YMC 20% C_{18} column. TLC: R_f = 0.3 (2:1 hexane/ethyl acetate). MS: $(M + H)^+$ 586, $(M + H - Boc)^+$ 486. $[\alpha]_D$ = −16.6° (c = 1.32, CH_3OH). IR (KBr): 3306, 2956, 2927, 2853, 1690, 1650, 1524, 1451, 1391, 1368, 1273, 1252, 1169, 1143, 1094, 699. ^1H NMR ($CDCl_3$): 1.4 and 1.42 (s, 9 H), 0.75–1.9 (m, 22 H), 3.1 (m, 2 H), 3.8–4.7 (m, 4 H), 4.9 and 5.05 (m, 1 H), 6.2–6.4 (m, 1 H), 6.7 (m, 1 H), 7.15–7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$): 22.0, 22.4, 22.6, 24.5, 24.6, 25.9, 26.1, 26.3, 28.1, 31.7, 31.9, 33.9, 34.0, 35.1, 40.5, 40.8, 47.9, 52.0, 52.4, 80.6, 126.9, 128.5, 128.6, 129.1, 136.2, 171.9, 172.2, 172.6, 172.8. Anal. Calcd for $C_{30}H_{46}N_3O_5F_3$: C, 61.52; H, 7.92; N, 7.18; F, 9.73. Found: C, 61.66; H, 8.04; N, 7.11; F, 9.56.

***N*-[1-(Cyclohexylmethyl)-3,3,3-trifluoro-2-oxopropyl]-*N*²-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide** (13). A solution of the alcohol **12** (585 mg, 1 mmol) in CH_2Cl_2 was added to a solution of Dess–Martin periodinane reagent (1.275 g, 3 mmol) and tBuOH (0.3 mL, 4 mmol) in CH_2Cl_2 (40 mL). After 12 h at room temperature, the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was suspended in EtOAc (15 mL) and the excess reagent was removed by filtration through Celite. Reconcentration of the filtrate gave the crude product which was purified by flash chromatography (3:1 hexane/EtOAc) to give 539 mg (92.5%) pure **13**. Mp: 148–153 °C. TLC: R_f = 0.27 (2:1 hexane/ethyl acetate). HPLC: t_R = 20.91 (47.2%), 22.8 (44.5%), 50 min; 50–90% aqueous CH_3CN gradient, flow rate 1 mL/min; YMC 20% C_{18} column. MS: $(M + H)^+$ 584. $[\alpha]_D$ = −20.4° (c = 1.1, CH_3OH). IR (KBr): 3301, 2957, 2927, 1690, 1651, 1525, 1451, 1392, 1368, 1251, 1173, 1143, 398. ^1H NMR (DMSO-d_6): 0.95 (m, 6 H), 1.42 (s, 9 H), 0.75–1.85 (m, 16 H), 3.1 (m, 2 H), 4.1–4.5 (m, 2 H), 4.85 (m, 1 H), 7.15–7.37 (m, 5 H), 7.5 and 7.72 (2d, 1 H, J = 7), 7.95 and 8.02 (2d, 1 H, J = 7), 8.68 (d, 1 H, J = 7). ^{13}C NMR (CD_3OD): 22.2, 22.3, 22.6, 23.1, 23.3, 25.5, 25.7, 27.0, 27.4, 27.5, 28.6, 32.8, 32.9, 34.8, 35.0, 35.2, 35.5, 36.3, 36.7, 39.1, 41.8, 41.9, 51.5, 51.8, 52.9, 53.0, 53.6, 57.0, 80.5, 97.1, 94.8 (q, J = 30), 97.3 (q, J = 28), 125.7 (q, J = 297), 127.5, 129.3, 130.2, 138.4, 157.4, 173.9, 174.1, 174.2, 174.4. Anal. Calcd for $C_{30}H_{44}N_3O_5F_3 \cdot 0.5H_2O$: C, 60.79; H, 7.65; N, 7.09; F, 9.62. Found: C, 60.94; H, 7.65; N, 7.00; F, 9.71.

(*R)-*N*-[1-(Cyclohexylmethyl)-2-methoxy-2-oxoethyl]-*N*²-[(phenylmethoxy)carbonyl]-L-leucinamide** (15). Amine **14**[9] (891 mg, 2.98 mmol) was added to a solution of Cbz-Leu-OH (789 mg, 2.98 mmol) in THF (12 mL). The solution was cooled to 0 °C, and HOBt (456 mg, 2.98 mmol) was added. After 2 min, iPr_2NEt (518.5 μL, 2.98 mmol) was added and this was followed immediately by addition of DCC (614 mg, 2.98 mmol). The reaction was stirred at 0 °C and left for overnight stirring at room temperature. Next day, the precipitated urea was filtered off and the filtrate concentrated to give an oil which was taken up in EtOAc (40 mL) and washed sequentially with $NaHCO_3$ (1 × 20 mL) and NaCl (1 × 20 mL). Drying and concentration gave an oily residue which after flash chromatographic purification (silica gel, 4:1 Hex/EtOAc) yielded **15** (832 mg, 64%). TLC: R_f = 0.48 (1:1 hexane/ethyl acetate). Mp: 76–79 °C. $[\alpha]_D$ = −33.8° (c = 1.34, CH_3OH). MS: $(M + H)^+$ 433. ^1H NMR ($CDCl_3$): 0.7–1.8 (m, 22 H), 3.7 (s, 3 H), 4.1–4.25 (br m, 1 H), 4.6 (m, 1 H), 5.12 (s, 2 H), 5.25 (d, 1 H, J = 8), 6.38 (d, 1 H, J = 8), 7.33 (br s, 5 H). ^{13}C NMR ($CDCl_3$): 22.1, 22.8, 24.6, 26.0, 26.1, 26.3, 32.5, 33.4, 34.9, 39.9, 41.3, 50.1, 52.2, 53.5, 67.9, 127.9, 128.1, 128.2, 128.5, 136.1, 156.1, 171.8, 173.1.

(*R)-*N*-[1-(Cyclohexylmethyl)-2-hydroxy-2-oxoethyl]-*N*²-[(phenylmethoxy)carbonyl]-L-leucinamide** (16). NaOH (1 N, 2 mL, 2 mmol) was added to solution of **15** in methanol (13 mL). A TLC check after 5 h at room temperature revealed completion of reaction. Solvents were stripped down on a rotary evaporator and the residue was partitioned between 50 mL of 1:1 EtOAc/1 N HCl. The aqueous layer was reextracted with EtOAc (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography eluting with 9:1:0.1 $CHCl_3$/MeOH/AcOH to give **16** (688 mg, 94.8%). TLC: R_f = 0.35 (9:1:0.1 $CHCl_3$/MeOH/AcOH). Mp: 55–66 °C. $[\alpha]_D$ = −23.7° (c = 2.0, MeOH). MS: $(M + H)^+$ 419. ^1H NMR (CD_3OD): 0.7–1.9 (m, 22 H), 3.7 (s, 3 H), 4.2 (br m, 1 H), 4.48 (br m, 1 H), 4.9 (s, 2 H), 7.3 (br s, 5 H). ^{13}C NMR (CD_3OD): 22.1, 23.4, 25.8, 27.1, 27.3, 27.5, 33.3, 34.8, 35.3, 40.2, 42.1, 42.4, 51.3, 54.7, 67.6, 128.7, 129.1, 129.4, 138.1, 158.2, 175.1, 175.9.

***N*-[1-(Cyclohexylmethyl)-3-ethoxy-2,3-dioxopropyl]-*N*²-[(phenylmethoxy)carbonyl]-L-leucinamide** (17). DMAP (8.5 mg) was added to a 1:1 THF/DMF solution (8.4 mL) of the acid **16** (585.2 mg, 1.4 mmol) and this was followed by addition of pyridine (453 μL, 5.6 mmol). After 5 min, ethyl oxalyl chloride (313.6 μL, 2.8 mmol) was added and the reaction mixture set to reflux for 2 h, then cooled to room temperature, and quenched with 1 mL of H_2O. After an additional 15 min of stirring, THF was stripped down and the residue taken in H_2O (25 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with NaCl (1 × 25 mL), dried (Na_2SO_4), and concentrated to give 881 mg of residue which was stirred overnight in 20 mL of EtOH with 1 g of solid $NaHCO_3$. Next day, the solid was filtered off and the filtrate concentrated to give an oily residue which after chromatographic purification yielded **17** (270 mg, 40.6%) as a 1:1 mixture of diastereomers. TLC: R_f = 0.47 (1:1 hexane/ethyl acetate). $[\alpha]_D$ = −6.1° (c = 1.44, MeOH). MS: $(M + H)^+$ 475. IR: 3310, 3303, 2955, 2926, 1730, 1661, 1535, 1449, 1285, 1262, 1244, 1049, 1029, 412, 405, 400. ^1H NMR ($CDCl_3$): 0.7–1.9 (m, 25 H), 4.25 (br m, 3 H), 5.1 (s, 2 H), 5.0–5.5 (m, 2 H), 6.7–7.0 (m, 1 H), 7.3 (s, 5 H). ^{13}C NMR (CD_3OD) : 13.9, 22.0, 22.7, 24.5, 24.7, 25.8, 26.0, 26.2, 32.1, 33.7, 34.2, 34.3, 37.9, 38.0, 40.9, 41.1, 41.3, 41.4, 53.2, 53.6, 62.5, 67.0, 127.8, 128.0, 128.4, 136.0, 156.2, 160.3, 172.2. Anal. Calcd for $C_{26}H_{38}N_2O_6$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.43; H, 8.03; N, 5.90.

(R*)-N-[1-(Cyclohexylmethyl)-2-methoxy-2-oxoethyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (18). 6 (2.017 g, 5.33 mmol) was dissolved in 20 mL of 1:1 DMF/THF and amine 14 (1.595 g, 5.33 mmol) was added. The solution was cooled to 0 °C and HOBt (0.815 g, 5.33 mmol) was added. After 2 min, iPr_2NEt (0.927 mL, 5.33 mmol) was added and this was followed immediately by addition of DCC (1.099 g, 5.33 mmol). The reaction was stirred at 0 °C for 2 h and left for stirring overnight at room temperature. Next day, the precipitated urea was filtered off and the filtrate concentrated to give an oil which was taken up in EtOAc (100 mL). The precipitated urea was refiltered and the filtrate was washed sequentially with $NaHCO_3$ (1 × 50 mL), 10% aqueous citric acid (2 × 50 mL), and $NaHCO_3$ (1 × 50 mL), dried; and concentrated to give 3.08 g crude product. Flash chromatographic purification eluting with 4:1 Hex/EtOAc yielded 18 (2.673 g, 92.2% yield). The reaction was repeated on a 30 mmol scale to provide additional amounts of 18 (15.89 g, 97%). Mp: 134–138 °C. TLC: R_f = 0.45 (1:1 hexane/ethyl acetate). $[\alpha]_D$ = −31.4° (c = 1.02 MeOH). MS: $(M + H)^+$ 546⁺. ^1H NMR ($CDCl_3$): 0.9 (d, 6 H, J = 6), 1.42 (s, 9 H), 0.8–1.8 (m, 16 H), 2.95–3.15 (m, 2 H), 3.71 (s, 3 H), 4.25–4.65 (m, 3 H), 5.08 (d, 1 H, J = 8), 6.58 (d, 1 H, J = 8), 6.65 (d, 1 H, J = 8), 7.15–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 22.1, 22.8, 24.5, 26.0, 26.3, 25.9, 28.2, 32.5, 33.3, 34.0, 37.9, 39.7, 41.0, 50.2, 51.7, 52.1, 55.7, 80.3, 126.8, 128.5, 129.2, 136.5, 155.4, 171.3, 173.0. Anal. Calcd for $C_{30}H_{47}N_3O_6$: C, 66.03; H, 8.68; N, 7.70. Found: C, 65.79; H, 8.61; N, 7.61.

(R*)-N-[1-(Cyclohexylmethyl)-2-hydroxy-2-oxoethyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (19). NaOH (1 N,35 mL, 35 mmol) was added to a solution of methyl ester 18 (15.26 g, 28 mmol) in methanol (100 mL). After refluxing for 1 h, the reaction was judged to be complete by TLC. It was cooled to room temperature and acidified to pH = 4.5 using 10% HCl. MeOH was removed on the rotary evaporator and the remainder diluted with H_2O (250 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with saturated NaCl (1 × 100 mL), dried, and concentrated to give the crude acid which upon trituration with ether yielded pure 19 (14.35 g, 96.5%). Mp: 58–66 °C. TLC: R_f = 0.45 (1:1 hexane/ethyl acetate). $[\alpha]_D$ = −25.8° (c = 1.23, CH_3OH). MS: $(M+H)^+$ 532. ^1H NMR ($CDCl_3$): 0.88 (m, 6 H), 1.38 (s, 9 H), 0.7–1.82 (m, 16 H), 2.8–3.15 (m, 2 H), 4.3–4.6 (m, 3 H), 5.25 (br s, 1 H), 6.95 (br s, 1 H), 7.05–7.35 (m, 5 H), 10.0 (br s, 1 H). ^{13}C NMR ($CDCl_3$): 22.1, 22.7, 24.5, 26.0, 26.1, 26.3, 28.2, 32.5, 33.4, 34.1, 38.2, 39.5, 41.0, 50.5, 51.9, 55.5, 80.4, 126.9, 128.5, 129.3, 136.4, 155.6, 171.9, 172.1, 175.8. Anal. Calcd for $C_{29}H_{45}N_3O_6$: C, 65.51; H, 8.93; N, 7.90. Found: C, 64.98; H, 8.55; N, 7.87.

N-[1-(Cyclohexylmethyl)-3-ethoxy-2,3-dioxopropyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (20). DMAP (73 mg, 0.6 mmol) and pyridine (4.86 mL, 60 mmol) were added to a solution of acid 19 (6.372 g, 12 mmol) in 1:1 THF/DMF (72 mL). After 5 min, freshly distilled ethyl oxalyl chloride (2.688 mL, 24 mmol) was added, and the solution was heated to reflux for 2 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL) and stirred for 30 min. The solvents were stripped down and the residue was partitioned between 250 mL of H_2O and 250 mL of EtOAc. The aqueous layer was reextracted with EtOAc (2 × 250 mL), and the combined organic extracts were washed sequentially with H_2O (1 × 100 mL), 1% HCl (1 × 100 mL), and saturated NaCl (1 × 100 mL). Drying and concentration gave 7.21 g of residue which was dissolved in EtOH (200 mL) and stirred very rapidly overnight with solid $NaHCO_3$ (10 g). The next day, the reaction mixture was filtered and the filtrate concentrated to give a residue which upon flash chromatographic purification yielded 20 (3.93 g, 56%) as a diastereomeric mixture. Mp: 102–128 °C. TLC: R_f = 0.38 (1:1 hexane/ethyl acetate). $[\alpha]_D$ = −14.2° (c = 0.8, MeOH). MS: $(M + H)^+$ 588. IR: 3289, 2976, 2957, 2927, 2853, 1731, 1694, 1646, 1539, 1527, 1499, 1450, 1391, 1368, 1252, 1172, 1050, 700, 405, 400. ^1H NMR ($CDCl_3$): 0.7–1.9 (m, 34 H), 3.05 (m, 2 H), 4.3 (m, 2 H), 4.2–4.55 (m, 2 H), 5.1 (br m, 2 H), 6.45 and 6.6 (d, 1 H, J = 8), 6.9 and 7.05 (d, 1 H, J = 1 H), 7.1–7.32 (m, 5 H). ^{13}C NMR ($CDCl_3$): 13.8, 21.7, 21.9, 22.0, 22.7, 22.8, 24.2, 24.4, 24.6, 25.8, 26.0, 26.1, 26.2, 28.1, 32.0, 32.2, 33.6, 34.1, 34.2, 37.4, 37.5, 37.57, 37.7, 37.8, 38.0, 40.4, 40.7, 40.8, 51.5, 53.5, 53.6, 56.1, 62.4, 62.5, 80.4, 80.8, 126.8, 126.9, 127.0, 128.6, 128.7, 129.1, 129.2, 136.3, 160.3, 160.4, 171.4, 171.5, 171.6, 192.5. Anal. Calcd for $C_{32}H_{49}N_3O_7$: C, 65.39; H, 8.40; N, 7.15. Found: C, 65.12; H, 8.45; N, 7.14.

N-[1-(Cyclohexylmethyl)-3-hydroxy-2,3-dioxopropyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (21). The α-keto ester 20 (171 mg, 0.29 mmol) was dissolved in ethanol (2 mL) and treated with 1 M K_2CO_3 (0.3 mL, 0.3 mmol). The reaction mixture was stirred at room temperature and a TLC check after 1 h revealed completion of reaction. The solvents were stripped down, the residue was taken up in 20 mL of 1:1 H_2O/EtOAc and acidified to pH = 4.0 with 10% HCl, and the two layers were separated. The aqueous layer was reextracted with EtOAc (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 117 mg of crude product which after flash chromatographic purification eluting with 9:1:0.1 $CHCl_3$/MeOH/AcOH yielded pure acid 21 (77 mg, 48%). Mp: 97–110 °C. TLC: R_f = 0.43 (9:1:0.1 $CHCl_3$/MeOH/AcOH). $[\alpha]_D$ = −11.4° (c = 0.42, MeOH). MS: $(M + H)^+$ 560. IR: 3424, 3415, 3409, 3404, 3396, 3385, 3321, 3312, 3302, 2956, 2927, 2853, 1650, 1525, 1499, 1451, 1421, 1416, 1392, 1368, 1252, 1170, 422, 412, 404. ^1H NMR ($CDCl_3$): 0.7–1.9 (m, 31 H), 2.7–3.15 (m, 2 H), 4.2–4.5 (m, 3 H), 7.25 (br s, 5 H). ^{13}C NMR ($CDCl_3$): 22.2, 23.4, 25.7, 27.2, 27.3, 27.5, 28.6, 33.2, 33.3, 34.1, 34.8, 35.3, 35.5, 39.0, 40.4, 42.1, 51.0, 51.7, 52.8, 53.0, 57.2, 57.5, 57.9, 80.6, 116.8, 127.6, 127.7, 129.3, 130.3, 138.5, 138.6, 157.5, 166.5, 174.1, 174.2. Anal. Calcd for $C_{30}H_{45}N_3O_7$: C, 64.38; H, 8.10; N, 7.51. Found: C, 64.56; H, 8.50; N, 7.74.

[R-(R*,S*)]- and [S-(R*,R*)]-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-[tris(methylthio)methyl]cyclohexanepropanol (22 and 23). nBuLi (50 mL of a 2.5 M solution, 125 mmol) was added over a period of 10 min to a solution of tris(methylthio)methane (20.37 g, 132 mmol) in 200 mL THF at −75 °C. A white precipitation occurs but smooth stirring could be maintained. After 20 min, aldehyde 2 (13.9 g, 54.5 mmol) was added as 150 mL of a THF solution at −70 to −65 °C. During the later half of the addition, the precipitation disappeared and a clear yellow solution resulted after the addition was complete. The reaction was continued for 3 h at −50 to −40 °C after which it was quenched with 100 mL of saturated NH_4Cl and warmed to room temperature. The two layers were separated; the aqueous layer was diluted with 200 mL of H_2O to dissolve the precipitated NH_4Cl and extracted with ether (2 × 100 mL). The organic solutions were combined, washed with saturated NaCl (1 × 150 mL), dried (Na_2SO_4), and concentrated to give 34.63 g of solid. The crude product yielded 7.57 g of pure diastereomer 22 (33.65%) upon crystallization from 6:1 hexane/ethyl ether. Mp: 147–149 °C. TLC: R_f = 0.29 (1:1 hexane/Et_2O). $[\alpha]_D$ = −12.4° (c = 1.33, MeOH). MS: $(M + H)^+$ 410. ^1H NMR ($CDCl_3$): 0.7–2.3 (m, 13 H), 1.45 (s, 9 H), 2.22 (s, 9 H), 3.5 (s, 1 H), 3.7 (br s, 1 H), 4.15 (m, 1 H), 5.1 (br s, 1 H). ^{13}C NMR ($CDCl_3$): 13.9, 26.2, 26.3, 26.6, 28.5, 33.1, 33.4, 34.2, 43.7, 47.9, 74.5, 78.8, 155.4. Anal. Calcd for $C_{18}H_{35}NO_3S_3$: C, 52.77; H, 8.61; N, 3.42; S, 23.48. Found: C, 52.60; H, 8.56; N, 3.36; S, 23.38.

The mother liquor was concentrated and the residue chromatographed by eluting with 4:1 to 2:1 hexane/Et_2O to give an additional 6.5 g of diastereomeric mixture of α-hydroxy ortho thioesters 22 and 23 (overall yield, 62.5%).

[R-(R*,S*)]-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-hydroxycyclohexanebutanoic Acid, Ethyl Ester (24). $HgCl_2$ (6.278 g, 23.1 mmol) and HgO (2.50 g, 11.56 mmol) were added to a solution of α-hydroxy ortho thioester 22 (1.891 g, 4.625 mmol) in 95% aqueous EtOH (115 mL). After stirring for 72 h at room temperature, the reaction mixture was filtered through Celite and the solid was washed with dichloromethane (50 mL). The filtrate was treated with H_2O (100 mL), and the two layers were separated. The aqueous layer was reextracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed sequentially with saturated NH_4Cl (2 × 100 mL), 75% NH_4OAc (1 × 100 mL), and saturated NaCl (1 × 100 mL), dried over Na_2SO_4, and filtered through Celite. The filtrate was concentrated and the residue chromatographed by eluting with 4:1 to 1:1 Hex/Et_2O to give pure 24 (1.246 g, 82%). TLC: R_f = 0.27 (1:1 hexane/Et_2O). $[\alpha]_D$ = −42.6° (c = 2.39, MeOH). MS: $(M + H)^+$ 330. ^1H NMR ($CDCl_3$): 0.8–1.95 (m, 13 H), 1.3 (t, J

= 7, 3 H) 1.4 (s, 9 H), 3.15 (d, 1 H, J = 7), 4.0-4.3 (m, 4 H), 4.63 (d, J = 9, 1 H). ^{13}C NMR ($CDCl_3$): 14.0, 26.1, 26.3, 26.4, 28.2, 32.8, 33.5, 34.2, 39.8, 50.3, 62.0, 72.4, 79.0, 155.2, 173.7.

[*R*-(*R,*S**)]- and [*S*-(*R**,*R**)]-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-hydroxycyclohexanebutanoic Acid, Ethyl Ester (24 and 25).** Mercury(II) chloride (7.35 g, 27.08 mmol) and mercury(II) oxide (2.93 g, 13.54 mmol) were added to a solution of diastereomeric mixture of α-hydroxy ortho thioesters **22** and **23** (2.77 g, 6.77 mmol) in 95% aqueous EtOH (175 mL). After stirring for 36 h at 25 °C, the reaction mixture was filtered through Celite and the solids were washed with additional EtOH (30 mL). The filtrate was diluted with chloroform (250 mL), and the organic solution was washed with saturated aqueous NH_4Cl (2 × 100 mL) and 75% aqueous NH_4OAc (1 × 100 mL), dried, and concentrated to give 2.56 g of crude product. Chromatographic purification eluting with 4:1 to 2:1 hexane/ether yielded **24** as the fast moving isomer (1.225 g, 55%, R_f = 0.27 in 1:1 hexane/ether) and **25** as the slow moving Isomer (356 mg, 16%, R_f = 0.17 in 1:1 hexane/ether). The data for **25** is as follows. MS: $(M + H)^+$ 330. ^{1}H NMR ($CDCl_3$): 0.8–1.85 (m, 13 H), 1.23 (t, J = 7, 3 H) 1.38 (s, 9 H), 3.18 (d, J = 5, 1 H), 4.0–4.3 (m, 4 H), 4.75 (d, J = 9, 1 H). ^{13}C NMR ($CDCl_3$): 14.2, 26.0, 26.3, 26.4, 28.3, 32.3, 33.8, 34.2, 36.7, 50.5, 61.8, 73.4, 79.5, 155.6, 173.0.

(4*S*-*trans*)-4-(Cyclohexylmethyl)-2-oxo-5-oxazolidinecarboxylic Acid, Ethyl Ester (26). Anhydrous HCl in dioxane (4 M, 0.5 mL) was added to a solution of **24** (31 mg, 0.094 mmol) in EtOAc (1 mL). TLC check after 4 h revealed total disappearance of starting material. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in THF (1 mL). iPr_2NEt (30 μL) and CDI (25 mg) were added to the solution, and the reaction was left for overnight stirring at room temperature. The next day, the reaction mixture was concentrated to give a residue which was dissolved in EtOAc (30 mL) and washed sequentially with saturated $NaHCO_3$ (1 × 15 mL), 10% HCl (2 × 15 mL), and saturated NaCl (1 × 15 mL). Drying and concentration gave a residue which was purified by flash chromatography to give pure **26** (18 mg, 75%). TLC: R_f = 0.37 (1:1 hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 0.8–1.8 (m, 13 H), 1.32 (t, J = 7, 3 H) 3.95 (m, 1 H), 4.3 (q, J = 7, 2 H), 4.55 (d, J = 5, 1 H), 6.31 (s, 1 H). ^{13}C NMR ($CDCl_3$): 14.1, 25.9, 26.0, 26.2, 32.7, 33.3, 34.0, 43.7, 53.8, 62.2, 78.3, 158.1, 168.8.

(4*S*-*cis*)-4-(Cyclohexylmethyl)-2-oxo-5-oxazolidinecarboxylic Acid, Ethyl Ester (27). Anhydrous HCl in dioxane (4 M, 0.75 mL) was added to a solution of **25** (60 mg, 0.182 mmol) in EtOAc (1 mL). TLC check after 1 h revealed total disappearance of starting material. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in THF (1.5 mL). iPr_2NEt (48 μL, 0.273 mmol) and CDI (38.3 mg, 0.237 mmol) were added to the solution, and the reaction was left for overnight stirring at room temperature. The next day, the reaction mixture was concentrated to give a residue which was dissolved in EtOAc (45 mL) and washed sequentially with saturated $NaHCO_3$ (1 × 15 mL), 10% HCl (2 × 20 mL), and saturated NaCl (1 × 15 mL). Drying and concentration gave 55 mg of residue which was purified by flash chromatography to give pure **27** (30 mg, 65%). ^{1}H NMR ($CDCl_3$): 0.8–1.8 (m, 13 H), 1.35 (t, J = 7, 3 H) 4.1–4.3 (m, 3 H), 5.04 (d, J = 8.5, 1 H), 6.4 (s, 1 H). ^{13}C NMR ($CDCl_3$): 14.1, 25.7, 26.0, 26.2, 31.9, 34.0, 34.2, 38.0, 52.0, 61.8, 76.7, 158.3, 167.2.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-3-ethoxy-2-hydroxy-3-oxopropyl]-*N*²-[(1,1-dimethylethoxy)carbonyl]-L-leucinamide (28).** The α-hydroxy ester **24** (1.245 g, 3.787 mmol) was treated with 1:1 TFA/CH_2Cl_2 (20 mL) at room temperature, and a TLC check after 15 min revealed completion of the reaction. The reaction mixture was filtered through a short cotton plug and the filtrate concentrated to give a residue which was taken up in MeOH (15 mL) and refiltered through a short pad of Celite to remove the precipitated impurities. The filtrate was reconcentrated to give the amine salt as a yellow-colored clear oil (1.285 g), which was dissolved in THF (10 mL) and treated with iPr_2NEt (717 μL, 3.75 mmol). In a separate flask, HOBt (574 mg, 3.75 mmol) and DCC (774 mg, 3.75 mmol) were sequentially added to a solution of BOC-Leu-OH hydrate (935 mg, 3.75 mmol) in DMF (10 mL) at 0 °C. After 20 min of stirring at room temperature, a premixed THF solution of the amine salt and iPr_2NEt prepared above was added to the reaction mixture. The reaction was stirred at 0 °C for 2 h and then left for overnight stirring at room temperature. Next day, the precipitated urea was filtered and the filtrate concentrated to give a residue that was taken up in EtOAc (100 mL) and washed sequentially with H_2O (2 × 25 mL), 10% citric acid (1 × 25 mL), saturated $NaHCO_3$ (1 × 25 mL), and saturated NaCl (1 × 25 mL). Drying (Na_2SO_4) and concentration afforded 1.39 g crude product which after chromatographic purification eluting with 3:1 hexane/EtOAc yielded pure **28** (823 mg, 50%). TLC: R_f = 0.25 (2:1 hexane/EtOAc). MS: $(M + H)^+$ 443. ^{1}H NMR ($CDCl_3$): 0.7–1.9 (m, 16 H), 0.9 (m, 6 H), 1.3 (t, J = 7, 3 H) 1.45 (s, 9 H), 3.42 (d, J = 5, 1 H), 4.0 (m, 1 H), 4.15 (m, 1 H), 4.2 (q, J = 7, 2 H), 4.47 (m, 1 H), 4.95 (br s, 1 H), 6.27 (d, J = 10, 1 H). ^{13}C NMR ($CDCl_3$): 14.0, 22.0, 22.7, 24.6, 26.0, 26.2, 26.4, 28.2, 32.7, 33.5, 34.8, 39.4, 41.2, 48.8, 53.2, 62.1, 72.1, 79.9, 155.5, 171.9, 173.4. Anal. Calcd for $C_{23}H_{42}N_2O_6$: C, 62.42; H, 9.57; N, 6.33. Found: C, 62.45; H, 9.53; N, 6.29.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-3-ethoxy-2-hydroxy-3-oxopropyl]-*N*²-[4-morpholino-1,4-dioxo-2-(phenylmethyl)butyl]-L-leucinamide (30).** **28** (395 mg, 0.892 mmol) was dissolved in EtOAc (5 mL) and treated for 30 min with 3 N HCl/AcOH. The solvents were removed on a rotary evaporator to give a residue which upon crystallization from MeOH/AcOH (1:8) gave the amine hydrochloride (240 mg, 71%). DCC (232 mg, 1.126 mmol), iPr_2NEt (216 mL, 1.126 mmol), and HOBt (172 mg, 1.126 mmol) were sequentially added to a solution of acid **29**[31] (312 mg, 1.126 mmol) and amine salt prepared above (427 mg, 1.126 mmol) in DMF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h and then left for overnight stirring at room temperature. The next day, the precipitated urea was filtered off, the filtrate was diluted with EtOAc (30 mL), and the organic solution was washed sequentially with H_2O (2 × 25 mL), 10% citric acid (1 × 25 mL), saturated $NaHCO_3$ (1 × 25 mL) and saturated NaCl (1 × 20 mL). Drying (Na_2SO_4) and concentration afforded 555 mg of crude product which upon flash chromatographic purification eluting with 19:19:1:0.05 Et_2O/$CHCl_3$/MeOH/NH_4OH yielded pure **30** (505 mg, 74.5%, overall yield from **28**, 53%). Mp: 75–87 °C. TLC: R_f = 0.55 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). $[\alpha]_D$ = −50.4° (c = 1.02, MeOH). MS: $(M + H)^+$ 602. IR: 3311, 2955, 2924, 2853, 1741, 1640, 1540, 1447, 1387, 1367, 1270, 1235, 1216, 1203, 1148, 1116, 1030, 700. ^{1}H NMR ($CDCl_3$): 0.7–1.9 (m, 25 H), 2.35 (s, 1 H), 2.6–2.8 (m, 2 H), 2.95–3.2 (m, 2 H), 3.2–3.4 (m, 2 H), 3.45–3.7 (m, 6 H), 3.8 (d, J = 7, 1 H), 4.0–4.25 (m, 4 H), 4.45 (m, 1 H), 6.5–6.65 (m, 2 H), 7.0–7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$): 14.0, 21.7, 22.8, 24.5, 26.0, 26.2, 26.4, 32.8, 33.4, 34.0, 34.2, 37.8, 39.0, 40.3, 42.0, 43.8, 45.6, 49.8, 52.6, 61.8, 66.3, 66.6, 72.1, 126.5, 128.5, 128.8, 138.5, 170.0, 171.3, 173.2, 174.7. Anal. Calcd for $C_{33}H_{51}N_3O_7$: C, 65.86; H, 8.54; N, 6.98. Found: C, 65.73; H, 8.64; N, 6.75.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-3-ethoxy-2,2-dihydroxy-3-oxopropyl]-*N*²-[4-morpholino-1,4-dioxo-2-(phenylmethyl)butyl]-L-leucinamide (31).** Dess–Martin reagent (310 mg, 0.75 mmol) was added in one portion to a solution of the α-hydroxy ester **30** (294 mg, 0.488 mmol) and *tert*-butyl alcohol (55 mg, 0.75 mmol) in dichloromethane 924 mL), and the reaction mixture was stirred overnight at room temperature. The next day, the reaction was judged to be complete by TLC, (total reaction time = 19 h). The solvents were removed on rotary evaporator, and the residue was dissolved in ethyl acetate (25 mL) and washed (3 × 10 mL) with an aqueous solution of $NaHCO_3$/$Na_2S_2O_3$ (500 mg of $Na_2S_2O_3$ dissolved in 30 mL of saturated $NaHCO_3$) to remove the excess reagent. Drying (Na_2SO_4), concentration, and chromatographic purification eluting with 40:1:0.05 $CHCl_3$/MeOH/NH_4OH afforded pure keto ester **31** (262 mg, 89.6%). TLC: R_f = 0.65 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). $[\alpha]_D$ = −19.24° (c = 1.0, MeOH). MS: $(M + H)^+$ 600. IR: 3427, 3423, 3405, 3395, 3295, 2955, 2925, 2854, 1731, 1641, 1539, 1498, 1463, 1448, 1297, 1271, 1236, 1116, 1068, 1048, 1031, 449, 434, 416, 410, 402, 399. ^{13}C NMR (CD_3OD): 14.3, 22.2, 23.4, 25.5, 27.0, 27.2, 27.4, 33.1, 34.8, 35.2, 38.1, 39.5, 41.7, 43.2, 45.5, 47.0, 52.9, 53.1, 54.7, 63.4, 67.5, 127.5, 129.4, 130.1, 140.0, 162.1, 171.9, 174.6, 176.8, 193.9. Anal. Calcd for $C_{33}H_{49}N_3O_7$: C, 66.08; H, 8.23; N, 7.01. Found: C, 66.34; H, 8.43; N, 7.06.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-3-ethoxy-2-hydroxy-3-oxopropyl]-*N*²-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-pheny-**

lalanyl]-L-leucinamide (32). The α-hydroxy ester **24** (625 mg, 1.89 mmol) was treated with 1:1 TFA/CH_2Cl_2 (20 mL) at room temperature, and a TLC check after 15 min revealed completion of the reaction. The reaction mixture was filtered through a short cotton plug, and the filtrate was concentrated to give a residue which was taken up in MeOH (10 mL), refiltered through a short pad of Celite to remove precipitated impurities, and reconcentrated to give the free amine salt as a yellow-colored clear oil (609 mg, 94%). iPr_2NEt (309.7 μL, 1.78 mmol) was added to a solution of the crude amine in THF (5 ml) at 0 °C. After 5 min, it was transferred to a flask containing a 0 °C DMF (5 mL) solution of **6** (672.8 mg, 1.78 mmol) and HOBt (272.3 mg, 1.78 mmol). After 5 min, DCC (367.3 mg, 1.78 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h, and then left for overnight stirring at room temperature. The next day, the reaction mixture was filtered through Celite, and concentrated, and the resulting residue was taken up in EtOAc (50 mL) and refiltered. The filtrate was washed sequentially with saturated $NaHCO_3$ (2 × 20 mL), 10% citric acid (1 × 20 mL), and saturated NaCl (1 × 25 mL), dried (Na_2SO_4), and concentrated to give 960 mg of residue. Chromatographic purification yielded pure **32** (752 mg, 71.7%, overall yield from **24**, 68%). Mp: 164–166 °C. TLC: R_f = 0.35 (1:1 hexane/EtOAc). $[\alpha]_D$ = −61.2° (*c* = 1.37, MeOH). MS: $(M + H)^+$ 590. IR (KBr): 3308, 2957, 2926, 2853, 1731, 1691, 1648, 1526, 1450, 1390, 1367, 1253, 1202, 1171. ^1H NMR ($CDCl_3$): 0.8–1.9 (m, 16 H), 0.88 (d, *J* = 7, 6 H), 1.3 (t, *J* = 7, 3 H), 1.42 (s, 9 H), 3.08 (m, 2 H), 3.68 (d, *J* = 5, 1 H), 4.0–4.5 (m, 6 H), 5.1 (d, *J* = 7, 1 H), 6.5 (m, 2 H), 7.1–7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$): 14.1, 22.0, 22.8, 24.6, 26.1, 26.2, 26.4, 28.2, 33.0, 33.3, 34.1, 37.7, 39.2, 41.2, 49.1, 52.1, 55.6, 55.8, 62.0, 72.0, 80.5, 126.9, 128.6, 129.2, 136.3, 155.6, 171.0, 171.2, 173.2. Anal. Calcd for $C_{32}H_{51}N_3O_7$: C, 65.17; H, 8.72; N, 7.12. Found: C, 65.25; H, 8.72; N, 7.09.

(*R,*R**)-*N*-[1-(Cyclohexylmethyl)-3-ethoxy-2-hydroxy-3-oxopropyl]-*N*²-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (33).** **23** (334 mg, 1.02 mmol) was dissolved in a solution of TFA/CH_2Cl_2 (1:1, 10 mL). After 15 min, the reaction mixture was filtered and concentrated, yielding the free amine (181 mg). A portion of the free amine (151 mg, 0.44 mmol) was treated with iPr_2 NEt (84.2 μL, 0.44 mmol) in DMF (3 mL). In a separate flask, HOBt (67 mg, 0.44 mmol) and DCC (90.7 mg. 0.44 mmol) were added sequentially to a 0 °C solution of **6** (166.8 mg, 0.44 mmol) in DMF (3 mL). After 5 min, the amine solution was transferred to this flask. After 16 h at 0 °C, the reaction mixture was filtered and concentrated to give a residue which was dissolved in EtOAc (20 mL) and washed sequentially with H_2O (3 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), 10% citric acid (10 mL), and saturated aqueous NaCl (10 mL). Drying and concentration gave 236 mg of crude product which after chromatographic purification and preparatory TLC afforded pure **33** (38 mg, 15%). Mp: 95–98 °C. TLC: R_f = 0.50 (9:1 $CHCl_3$/MeOH). $[\alpha]_D$ = −21.6° (*c* = 0.44, MeOH). MS: $(M + H)^+$ 590. IR (KBr): 3431, 2926, 2852, 1727, 1690, 1647, 1527, 1467, 1450, 1391, 1367, 1251, 1172, 1125, 1095, 1048, 1023, 699, 565, 536, 506, 490, 474, 459. ^1H NMR ($CDCl_3$): 0.8–1.85 (m, 16 H), 0.9 (d, *J* = 7, 6 H), 1.3 (t, *J* = 7, 3 H), 1.5 (s, 9 H), 3.1 (m, 2 H), 3.25 (br s, 1 H), 4.15–4.45 (m, 6 H), 4.9 (m, 1 H), 6.2–6.4 (m, 2 H), 7.15-7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 14.2, 22.0, 22.9, 24.7, 26.0, 26.2, 26.4, 28.2, 32.3, 33.9, 34.0, 36.3, 37.5, 40.9, 49.6, 52.4, 56.0, 61.8, 73.0, 80.6, 127.0, 128.7, 129.3, 136.5, 155.5, 171.6, 172.6. Anal. Calcd for $C_{32}H_{51}N_3O_7 \cdot 1.2H_2O$: C, 62.86; H, 8.80; N, 6.87. Found: C, 63.24; H, 9.01; N, 6.48.

***N*-[*N*-(Cyclopentylcarbonyl)-L-phenylalanyl]-L-leucine, Methyl Ester (34).** Compound **5** (12.01 g, 30.64 mmol) was treated with a solution of HCl in acetic acid (62 mL) for 1 h and concentrated to give an oily residue. It was triturated with toluene and concentrated to yield the dipeptide amine hydrochloride salt (10 g, 98%). A portion of this compound (5.0 g, 15.2 mmol), cyclopentane carboxylic acid (1.65 mL, 15.2 mmol), iPr_2NEt (2.93 mL, 17 mmol), and HOBt (2.33 g, 15.2 mmol) were dissolved in DMF (60 mL) and cooled to 0 °C. DCC (3.14 g, 15.2 mmol) was finally added, and after 16 h at 0 °C, the reaction mixture was filtered and the filtrate concentrated. The residue was taken up in EtOAc (250 mL) and washed sequentially with H_2O (3 × 150 mL), saturated $NaHCO_3$ (1 × 150 mL), 5% HCl (1 × 150 mL), and saturated NaCl (1 × 150 mL). Drying and concentration gave 6.0 g of crude product which after chromatographic purification eluting with 4:1 to 1:1 hexane/EtOAc afforded pure **34** (3.4 g, 57.6%). Mp: 170–171 °C. TLC: R_f = 0.41 (1:1 hexane/EtOAc). $[\alpha]_D$ = −23.9° (*c* = 1.18, MeOH). MS: $(M - H)^+$ 387. ^1H NMR ($CDCl_3$): 0.9 (d, 6 H, *J* = 6), 1.4–2.0 (m, 11 H), 2.5 (m, 1 H), 3.08 (d, 2 H, *J* = 8), 3.7 (s, 3 H), 4.5 (m, 1 H), 4.68 (m, 1 H), 6.05 (d, 1 H, *J* = 8), 6.28 (d, 1 H, *J* = 8), 7.15–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 21.8, 22.6, 24.7, 25.8, 29.9, 30.5, 38.1, 41.0, 45.4, 50.9, 52.1, 53.9, 126.7, 128.3, 129.4, 136.6, 171.4, 172.7, 176.3. Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.57; H, 8.31; N, 7.20.

***N*-[*N*-(Cyclopentylcarbonyl)-L-phenylalanyl]-L-leucine (35).** NaOH (1 N, 12.36 mL, 12.36 mmol) was added to a solution of **34** (2.04 g, 5.3 mmol) in MeOH (20 mL). After 5 h at room temperature, the reaction mixture was concentrated, and the residue was taken up in a mixture of H_2O (20 mL) and EtOAc (50 mL) and acidified to pH = 2. The layers were separated, and the aqueous solution was reextracted with EtOAc (3 × 75 mL). The combined organic extracts were dried and concentrated to yield **35** (1.84 g, 98.4%). Mp: 148–151 °C. $[\alpha]_D$ = −12.9° (*c* = 1.19, MeOH). MS: $[(M + H)^+ - H_2O]$ 357. ^1H NMR (CD_3OD): 0.95 (m, 6 H), 1.35–1.9 (m, 11 H), 2.6 (m, 1 H), 2.87 (dd, 1 H, *J* = 9, 14), 3.18 (dd, 1 H, *J* = 5, 14), 4.45 (m, 1 H), 4.71 (m, 1 H), 7.25 (m, 5 H). ^{13}C NMR ($CDCl_3$): 22.0, 23.4, 25.9, 26.7, 26.8, 30.9, 31.6, 38.9, 41.7, 46.1, 52.0, 55.4, 127.5, 129.2, 130.4, 138.4, 173.9, 175.7, 178.8. Anal. Calcd for $C_{21}H_{30}N_2O_4 \cdot 1.34H_2O$: C, 63.28; H, 8.26; N, 7.03. Found: C, 63.32; H, 7.87; N, 7.01.

[*R*-(*R,*S**)]-β-[[(1,1-Dimethylethoxy)carbonyl]amino]-α-(2-propyl-1,3-dithian-2-yl)cyclohexanepropanol (37).** nBuLi (2.5 M, 11.76 mL, 29.4 mmol) was added dropwise at −25 °C to a solution of 2-*n*-propyl-1,3-dithiane (**36**, 4.536 g, 28.0 mmol; D. Seebach et al. *Synthesis*, **1976**, 477) in THF (40 mL). After stirring for 2 h at −20 to −25 °C, the solution was cooled to −78 °C and aldehyde **2** (3.57 g, 14.0 mmol) in THF (20 mL) was added. The reaction mixture was warmed gradually from −78 to −50 °C over a period of 18 h and quenched with saturated NH_4Cl (50 mL), and the two layers were separated upon warming to room temperature. The aqueous layer was diluted with water (75 mL) to dissolve the precipitated NH_4Cl and reextracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated NaCl (1 × 75 mL), dried (Na_2SO_4), and concentrated to give the crude product (7.9 g) which, upon flash chromatographic purification eluting from 9:1 to 2:1 hexane/EtOAc, yielded pure **37** (1.517 g, 26%). The product appeared to be a single diastereomer by ^{13}C. TLC: R_f = 0.56 (1:1 hexane/ether). MS: $(M + H)^+$ 418. ^1H NMR ($CDCl_3$): 1.44 (m, 9 H), 0.8–2.15 (m, 22 H), 2.5–3.05 (m, 4H), 3.88 (s, 1 H), 4.37 (m, 1 H), 5.05 (d, 1 H, *J* = 8). ^{13}C NMR ($CDCl_3$): 14.5, 18.2, 24.3, 25.0, 26.0, 26.39, 26.47, 26.6, 28.4, 33.3, 34.5, 36.2, 44.9, 45.5, 59.1, 71.3, 78.6, 154.8. Anal. Calcd for $C_{21}H_{39}NO_3S_2$: C, 60.39; H, 9.41; N, 3.35. Found: C, 60.88; H, 9.31; N, 3.50.

[*R*-(*R,*S**)]-β-Amino-α-(2-propyl-1,3-dithian-2-yl)cyclohexanepropanol (38).** **37** (2.37 g, 5.7 mmol) was dissolved in a saturated solution anhydrous HCl in EtOAc (20 mL) and stirred for 1 h at 0 °C and 3 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue triturated with Et_2O. Filtration of the precipitated product and drying gave pure hydrochloride salt (1.493 g, 75%). TLC: R_f = 0.15 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). ^1H NMR (CD_3OD): 0.8–2.10 (m, 22 H), 2.75 (m, 2 H), 3.10 (m, 2 H), 3.76 (t, 1 H, *J* = 7), 3.93 (s, 1 H). ^{13}C NMR (CD_3OD): 14.6, 18.8, 25.6, 27.9, 27.3, 27.4, 27.7, 33.9, 34.4, 34.8, 40.0, 41.7, 50.3, 57.7, 75.6. Anal. Calcd for $C_{18}H_{31}NO_2S \cdot 1.0HCl$: C, 54.29; H, 9.11; N, 3.96; S, 18.11; Cl, 10.01. Found: C, 54.21; H, 9.17; N, 3.98; S, 18.03; Cl, 10.00.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-2-hydroxy-2-(2-propyl-1,3-dithian-2-yl)ethyl]-*N*²-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (39).** The amine hydrochloride salt **38** (388 mg, 1.1 mmol) and acid **6** (415.8 mg, 1.1 mmol) were dissolved in DMF (5 mL) and cooled to 0 °C. iPr_2NEt (191.4 μL, 1.1 mmol) was added and after 5 min, this was followed by sequential addition of HOBt (168.3 mg, 1.1 mmol) and DCC (227 mg, 1.1 mmol). The reaction mixture was left for overnight stirring with gradual warming to room temperature. The next day (total reaction time, 15 h), the reaction mixture was diluted with EtOAc (35 mL), the urea was filtered off, and the filtrate

was washed sequentially with H_2O (2 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), 10% citric acid (1 × 20 mL), and saturated NaCl (1 × 20 mL). Drying (Na_2SO_4) and concentration afforded crude product (821 mg) which, upon chromatographic purification eluting with 4:1 Hex/EtOAc, yielded (621 mg, 83.3%) pure **39**. Mp: 87–92 °C. TLC: R_f = 0.50 (1:1 hexane/EtOAc). $[\alpha]_D$ = −35.0° (c = 0.34, MeOH). MS: $(M + H)^+$ 678. IR (KBr):3421, 2957, 2924, 2870, 2851, 1651, 1513, 1468, 1451, 1388, 1367, 1275, 1250, 1169, 1081, 1050, 1023, 699. ^1H NMR ($CDCl_3$): 1.45 (m, 9 H), 0.8–2.15 (m, 31 H), 2.65 (m, 2 H), 2.9 (m, 2 H), 3.08 (m, 3 H), 3.95 (m, 1 H), 4.35 (m, 2 H), 4.55 (m, 1 H), 4.92 (m, 1 H), 6.35 (d, 1 H, J = 7), 6.45 (d, 1 H, J = 7), 7.15–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 14.3, 18.0, 21.6, 22.8, 23.9, 24.3, 24.9, 25.8, 26.1, 26.3, 28.0, 32.5, 33.5, 34.3, 35.7, 37.2, 41.2, 43.8, 44.6, 51.6, 55.5, 59.0, 70.7, 79.7, 126.5, 128.2, 129.1, 136.4, 155.1; 169.7, 170.9. Anal. Calcd for $C_{36}H_{59}N_3O_5S_2 \cdot 0.6H_2O$: C, 62.82; H, 8.81; N, 6.11; S, 9.32. Found: C, 62.84; H, 8.60; N, 6.00; S, 9.13.

(S*,R*)-N-[1-(Cyclohexylmethyl)-2-hydroxy-2-(2-propyl-1,3-dithian-2-yl)ethyl]-N²-[N-(cyclopentylcarbonyl)-L-phenylalanyl]-L-leucinamide (40). The amine hydrochloride **38** (707 mg, 2 mmol) was added to a solution of acid **35** (748 mg, 2 mmol) in THF (8 mL) and cooled to 0 °C. HOBt (306 mg, 2 mmol), iPr_2NEt (383 mL, 2.2 mmol), and DCC (413 mg, 2 mmol) were then sequentially added, and the reaction was stirred for 16 h at 0 °C. The reaction mixture was filtered and the filtrate concentrated to give a residue which was taken up in EtOAc (50 mL) and washed sequentially with H_2O (2 × 30 mL), saturated $NaHCO_3$ (2 × 40 mL), 10% citric acid (40 mL), and saturated NaCl (40 mL). Drying and concentration gave the crude product (1.2 g) which was purified by flash chromatography eluting from 9:1 to 4:1 Hex/EtOAc to give **40** (936 mg, 72%). Mp: 135–142 °C. TLC: R_f = 0.36 (1:1 hexane/EtOAc). $[\alpha]_D$ = −30.4° (c = 1.16, MeOH). MS: $(M + H)^+$ 674. ^1H NMR (CD_3OD): 0.9 (m, 9 H), 1.05–2.05 (m, 30 H), 2.5–2.7 (m, 3 H), 2.8–3.0 (m, 2 H), 3.2 (m, 2 H), 3.95 (s, 1 H), 4.4 (m, 1 H), 4.6–4.8 (m, 3 H), 7.20 (m, 1 H), 7.25 (s, 5 H), 7.4 (d, 1 H, J = 9), 7.88 (d, 1 H, J = 8). ^{13}C NMR ($CDCl_3$): 15.1, 19.2, 22.0, 23.6, 25.6, 25.7, 26.2, 26.9, 27.0, 27.4, 27.7, 30.9, 31.7, 34.5, 35.5, 37.7, 39.0, 41.8, 45.3, 46.1, 46.7, 49.6, 53.2, 55.5, 60.0, 73.5, 127.6, 129.3, 130.3, 138.6, 172.7, 173.9, 178.8. Anal. Calcd for $C_{37}H_{59}N_3O_4S_2$: C, 65.93; H, 8.82; N, 6.24; S, 9.51. Found: C, 65.70; H, 8.98; N, 5.98; S, 9.45.

(S*,R*)-N-[1-(Cyclohexylmethyl)-2-hydroxy-3-oxohexyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (41). Dithiane **39** (338.5 mg, 0.5 mmol) was dissolved in CH_3CN (12 mL) and diluted with H_2O (3 mL). $Ce(NH_4)_2(NO_3)_6$ (1.096 g, 2.0 mmol) was added to this solution, and after 20 min, the reaction mixture was diluted with water (40 mL) and extracted with ether (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 378 mg of residue which, upon chromatographic purification eluting with 3:1 hexane/EtOAc, yielded hydroxy ketone **41** (140 mg, 47.7%). Mp: 149–152 °C. TLC: R_f = 0.51 (1:1 hexane/EtOAc). MS: $(M + H)^+$ 588. ^1H NMR ($CDCl_3$): 0.87 (d, 6 H, J = 6), 0.93 (t, 3 H, J = 8), 1.38 (s, 9 H), 0.7–1.9 (m, 18 H), 2.47 (m, 1 H), 2.68 (m, 1 H), 3.07 (m, 2 H), 3.95 (d, 1 H, J = 4), 4.12 (d, 1 H, J = 4), 4.32 (m, 2 H), 4.55 (m, 1 H), 5.05 (d, 1 H, J = 7), 6.36 (d, 1 H, J = 9), 6.42 (d, 1 H, J = 8), 7.15–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 13.6, 16.8, 22.0, 22.6, 24.6, 26.0, 26.1, 26.4, 28.1, 33.0, 33.3, 34.1, 37.7, 39.7, 39.9, 41.2, 48.1, 52.0, 55.7, 77.7, 80.4, 126.9, 128.6, 129.2, 136.4, 155.5, 171.1, 210.2. Anal. Calcd for $C_{33}H_{53}N_3O_3$: C, 67.43; H, 9.09; N, 7.15. Found: C, 67.14; H, 9.40; N, 7.03.

(S*,R*)-N-[1-(Cyclohexylmethyl)-2-hydroxy-3-oxohexyl]-N²-[N-(cyclopentylcarbonyl)-L-phenylalanyl]-L-leucinamide (42). A solution of $Tl(NO_3)_3 \cdot 3H_2O$ (1.05 g, 1.18 mmol) in methanol (20 mL) was added to a solution of **40** (799 mg, 1.18 mmol) in MeOH (40 mL) and Et_2O (20 mL). After 10 min, the reaction mixture was filtered and concentrated, and the residue was partitioned between EtOAc (150 mL) and H_2O (100 mL). The aqueous layer was reextracted with EtOAc (2 × 120 mL). The combined organic extracts were washed with 10% citric acid (150 mL), dried, and concentrated, affording 2.5 g of crude compound. Purification by flash chromatography, eluting with 2:1 Hex/EtOAc, yielded **42** (573 mg, 83.4%). Mp: 169 °C decomposition. TLC: R_f = 0.40 (1:1 hexane/EtOAc). $[\alpha]_D$ = −61.3° (c = 1.19, MeOH). MS: $(M + H)^+$ 584. IR (KBr): 3290, 2956, 2925, 2869, 2853, 1714, 1640, 1541, 1449, 1398, 1369, 1230, 698, 422. ^1H NMR ($CDCl_3$): 0.88 (m, 6 H), 0.92 (t, 3 H, J = 7), 0.75–1.9 (m, 26 H), 2.35–2.55 (m, 2 H), 2.65–2.75 (m, 1 H), 3.07 (m, 2 H), 3.85 (m, 1 H), 4.12 (s, 1 H), 4.2 (m, 1 H), 4.47–4.7 (m, 2 H), 5.97 (d, 1 H, J = 7), 6.1 (d, 1 H, J = 9), 6.38 (d, 1 H, J = 8), 7.15–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 13.6, 16.8, 22.0, 22.7, 24.5, 25.9, 26.0, 26.3, 29.6, 30.8, 33.0, 33.2, 34.1, 38.4, 39.5, 39.9, 40.9, 45.1, 48.4, 52.1, 53.5, 77.6, 126.5, 128.2, 129.5, 136.6, 171.4, 171.9, 176.3, 210.6. Anal. Calcd for $C_{34}H_{53}N_3O_5 \cdot 0.63H_2O$: C, 68.62; H, 9.19; N, 7.06. Found: C, 68.79; H, 8.92; N, 6.99.

(R*)-N-[1-(Cyclohexylmethyl)-2,3-dioxohexyl]-N²-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-leucinamide (43). A solution of the hydroxy ketone **41** (58.7 mg, 0.1 mmol) in CH_2Cl_2 (3 mL) was added to a suspension of Dess–Martin periodinane (65 mg, 0.15 mmol) and tBuOH (12 mg, 0.15 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred vigorously, and after 6 h, additional Dess–Martin reagent (153 mg, 0.45 mmol) and tBuOH (35 mg, 0.45 mmol) were added along with 5 mL of CH_2Cl_2 and the reaction mixture left for overnight stirring. The next day, the reaction mixture was filtered through Celite, the filtrate was concentrated, and the residue was chromatographed, eluting with 2:1 hexane/EtOAc, to give pure **43** (51 mg, 87.2%). Mp: 134–143 °C. TLC: R_f = 0.44 (2:1 hexane/EtOAc). $[\alpha]_D$ = −36.6° (c = 0.61, MeOH). MS: $(M + H)^+$ 586. IR (KBr): 3294, 3065, 2960, 2928, 2873, 2854, 1713, 1691, 1645, 1526, 1451, 1390, 1367, 1315, 1266, 1252, 1170, 699, 422. ^1H NMR ($CDCl_3$): 0.88 (m, 9 H), 1.38 (s, 9 H), 0.7–1.85 (m, 18 H), 2.73 (m, 2 H), 3.07 (m, 2 H), 4.2–4.45 (m, 2 H), 4.75–5.0 (m, 2 H), 6.35 (m, 1 H), 6.78 (m, 1 H), 7.1–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): 13.5, 16.3, 21.8, 22.8, 24.5, 25.9, 26.0, 26.3, 28.2, 32.3, 33.6, 34.2, 37.7, 38.1, 40.5, 51.3, 51.8, 56.6, 80.6, 127.0, 128.7, 129.2, 136.2, 171.5, 197.2, 199.3. Anal. Calcd for $C_{33}H_{51}N_3O_6$: C, 67.66; H, 8.78; N, 7.18. Found: C, 67.52; H, 8.71; N, 7.13.

(R*)-N-[1-(Cyclohexylmethyl)-2,3-dioxohexyl]-N²-[N-(cyclopentylcarbonyl)-L-phenylalanyl]-L-leucinamide (44). A solution of the hydroxy ketone **42** (268 mg, 0.46 mmol) was added to a suspension of Dess–Martin reagent (389 mg, 0.91 mmol) and tBuOH (68 mg, 0.92 mmol) in CH_2Cl_2 (40 mL). After 5 h, the reaction mixture was filtered and concentrated, yielding 666 mg of crude product which was subjected to chromatographic purification, eluting with 2:1 Hex/EtOAc, to afford **44** (217 mg, 81.2%). Mp: 152–161 °C. TLC: R_f = 0.37 (1:1 hexane/EtOAc). $[\alpha]_D$ = −59.1° (c = 0.45, $CHCl_3$). MS: $(M + H)^+$ 582. IR (KBr): 3278, 2957, 2927, 2870, 2854, 1715, 1638, 1542, 1449, 1398, 1227. ^{13}C NMR ($CDCl_3$): 13.5, 16.3, 21.8, 22.9, 24.5, 25.9, 26.1, 26.3, 29.8, 30.8, 32.2, 33.3, 34.2, 37.5, 38.1, 38.8, 41.2, 44.9, 51.4, 51.8, 53.5, 126.4, 128.1, 129.3, 136.8, 172.0, 172.2, 176.3, 197.4, 199.4. Anal. Calcd for $C_{34}H_{51}N_3O_5 \cdot 1.0H_2O$: C, 70.19; H, 8.84; N, 7.22. Found: C, 70.12; H, 8.79; N, 7.12.

N-[(1,1-Dimethylethoxy)carbonyl]-1-[(4-methylphenyl)sulfonyl]-L-histidine (45). N-α-[Boc-L-Histidine (12.7 g; 50 mmol) was dissolved in a solution of Na_2CO_3 (10.6 g, 100 mmol) in 150 mL of H_2O and cooled to 10 °C. Tosyl chloride (12.8 g, 67 mmol) was added in very small portions over a period of 30 min while maintaining vigorous stirring and controlling the temperature between 10 and 15 °C. After the addition was complete, the reaction mixture was warmed to room temperature and stirring was continued for an additional 4 h. The reaction mixture was extracted with Et_2O (2 × 75 mL), and the organic portions were discarded. The aqueous layer was acidified to pH = 3.3 with 1 N HCl and extracted with EtOAc (2 × 150 mL), and the combined organic extracts were dried and concentrated to give an oily residue. Crystallization from EtOAc afforded pure **45** (9.42 g, 46%). Mp: 120 °C decomposition. TLC: R_f = 0.38 (9:1:0.1 $CHCl_3$/MeOH/AcOH). $[\alpha]_D$ = +15.3° (c = 1.66, CH_3OH). MS: $(M + H)^+$ 410. ^1H NMR ($CDCl_3$): 1.46 (s, 9 H), 2.45 (s, 3 H), 3.18 (s, 2 H), 4.45 (m, 1 H), 5.37 (m, 1 H), 7.1 (s, 1 H), 7.37 (d, 2 H, J = 8), 7.8 (d, 2 H, J = 8), 8.08 (s, 1 H). ^{13}C NMR ($CDCl_3$): 21.6, 28.2, 29.6, 52.5, 79.7, 115.6, 127.4, 130.4, 134.3, 136.8, 138.1, 146.6, 155.1, 172.7. Anal. Calcd for $C_{18}H_{23}N_3O_6S \cdot 0.14H_2O$: C, 52.48; H, 5.69; N, 10.20; S, 7.78. Found: C, 52.72; H, 5.70; N, 9.72; S, 8.09.

(S*,R*)-N-[1-(Cyclohexylmethyl)-2-hydroxy-2-(2-propyl-1,3-dithian-2-yl)ethyl]-N²-[(1,1-dimethylethoxy)carbonyl]-1-[(4-methylphenyl)sulfonyl]-L-histidinamide (46). Trieth-

ylamine (108 μL, 0.775 mmol) was added dropwise to a solution of the acid **45** (133 mg, 0.325 mmol) and the amine hydrochloride salt **38** (88.4 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After 5 min, diphenylphosphoryl azide (DPPA, 70 μL, 0.325 mmol) was added, and the reaction mixture was stirred for 2 h at 0 °C and then overnight at room temperature The next day, the reaction mixture was concentrated on a rotary evaporator to remove excess Et_3N, and the residue was partitioned between CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ (15 mL). The aqueous layer was reextracted (2 × 15 mL of CH_2Cl_2), and the combined organic extracts were dried (Na_2SO_4) and concentrated to give 292 mg residue. Chromatographic purification eluting with $CHCl_3$/MeOH/NH_4OH (19:1:0.05) gave pure **46** (125 mg, 71%) followed by the corresponding deprotected compound **47** (27 mg, 20%, R_f = 0.25, 9:1:0.05 $CHCl_3$/MeOH/NH_4OH). **47** could be conveniently converted to **46** (98% yield) by treatment with triethylamine (1.6 equiv) and *p*-toluenesulfonyl chloride (1.2 equiv) in dioxane for 15 min, followed by concentration and flash chromatography of the crude product. Characterization of **46**: Mp: 83–88 °C. TLC: R_f = 0.72 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). $[\alpha]_D$ = −16.5° (*c* = 1.3, MeOH). ^1H NMR ($CDCl_3$): 1.38 (s, 9 H), 0.8–2.1 (m, 22 H), 2.45 (s, 3 H), 2.47–3.1 (m, 6 H), 3.25 (s, 1 H), 3.9 (s, 1 H), 4.35 (m, 1 H), 4.55 (m, 1 H), 5.85 (m, 1 H), 6.93 (d, 1 H, *J* = 8), 7.1 (s, 1 H), 7.35 (d, 2 H, *J* = 7), 7.8 (d, 2 H, *J* = 7), 7.92 (s, 1 H). ^{13}C NMR ($CDCl_3$): 13.8, 14.1, 17.8, 21.3, 23.9, 24.7, 25.6, 25.9, 26.2, 27.9, 29.9, 32.5, 33.0, 34.0, 35.5, 43.7, 44.4, 53.5, 58.9, 71.0, 79.2, 114.4, 126.9, 130.0, 134.6, 135.8, 140.6, 145.8, 154.9, 169.0. Anal. Calcd for $C_{34}H_{52}N_4S_3O_6$: C, 57.60; H, 7.39; N, 7.90; S, 13.57. Found: C, 57.71; H, 7.48; N, 7.64; S, 13.71

Characterization of **47**: TLC: R_f = 0.25 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). MS: $(M + H)^+$ 555. ^1H NMR ($CDCl_3$): 1.44 (s, 9 H), 0.7–2.1 (m, 22 H), 2.4–3.2 (m, 6 H), 3.9 (s, 1 H), 4.32 (m, 1 H), 4.62 (m, 1 H), 5.63 (br m, 1 H), 6.85 (s, 1 H), 7.1 (m, 1 H), 7.55 (s, 1 H).

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-2-hydroxy-3-oxohexyl]-*N*²-[(1,1-dimethylethoxy)carbonyl]-1-[(4-methylphenyl)sulfonyl]-L-histidinamide (48).** $Tl(NO_3)_3 \cdot 3H_2O$ (844 mg, 1.9 mmol) was added in one portion to a solution of the dithiane **46** (674 mg, 0.95 mmol) in MeOH/Et_2O (1:1, 40 mL) at 0 °C. After 15 min, the reaction mixture was filtered through Celite, and the solids were washed with EtOAc (2 × 25 mL). Concentration of the solid gave a residue which upon chromatographic purification eluting from 2:1 to 1:1 hexane/EtOAc yielded **48** (399 mg, 67.9%). Mp: 67–76 °C. TLC: R_f = 0.24 (1:2 hexane/EtOAc). $[\alpha]_D$ = −42.6° (*c* = 1.21, MeOH). ^1H NMR ($CDCl_3$): 0.93 (t, 3 H, *J* = 7), 1.43 (s, 9 H), 0.8–1.85 (m, 15 H), 2.43 (s, 3 H), 2.3–3.0 (m, 4 H), 3.7–3.95 (m, 1 H), 4.05 (s, 1 H), 4.27 (m, 1 H), 4.52 (m, 1 H), 5.77 (d, 1 H, *J* = 7), 6.7 (m, 1 H), 7.12 (s, 1 H), 7.37 (d, 2 H, *J* = 8), 7.84 (d, 2 H, *J* = 8), 7.98 (s, 1 H). ^{13}C NMR ($CDCl_3$): 13.6, 16.9, 21.6, 25.9, 26.1, 26.4, 28.2, 30.4, 32.8, 33.3, 33.9, 39.7, 40.0, 48.0, 53.7, 77.9, 79.9, 114.8, 127.4, 130.3, 134.7, 136.1, 140.3, 146.3, 155.2, 170.7, 210.1. Anal. Calcd for $C_{31}H_{46}N_4O_7S \cdot 2.2H_2O$: C, 58.85; H, 7.57; N, 8.86. Found: C, 59.09; H, 7.47; N, 8.56.

(*S,*R**)-*N*-[1-(Cyclohexylmethyl)-2-hydroxy-3-oxohexyl]-*N*²-[(1,1-dimethylethoxy)carbonyl]-L-histidinamide (49).** HOBt (93 mg, 0.6 mmol) was added in one portion to a solution of hydroxy ketone **48** (93 mg, 0.15 mmol) in MeOH (3 mL). After 4 h, methanol was removed on a rotary evaporator and the residue chromatographed (20 g silica gel, 40:1:0.5 to 19:1:0.05 $CHCl_3$/MeOH/NH_4OH) to yield pure **49** (65 mg, 93%). HCl (1.0 N, 106.4 μL, 0.106 mmol) was added to a solution of **49** (52 mg, 0.112 mmol) in methanol (10 mL). After 5 min, the solvents were stripped down and the residue was lyophilized to give the hydrochloride salt of **49**. Mp: 95–150 °C. TLC: R_f = 0.16 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). $[\alpha]_D$ = −72.8° (*c* = 0.64, MeOH). MS: $(M + H)^+$ 465. IR (KBr): 3282, 2967, 2925, 2852, 1710, 1668, 1624, 1525, 1449, 1392, 1367, 1250, 1168, 1114, 1086, 1049, 1021, 627. ^1H NMR ($CDCl_3$): 0.95 (t, 3 H, *J* = 7), 1.43 (s, 9 H), 0.75–1.9 (m, 15 H), 2.4–3.0 (m, 4 H), 3.1–3.2 (m, 1 H), 4.3 (s, 1 H), 4.45–4.75 (m, 3 H), 5.65 (m, 1 H), 7.1 (m, 1 H), 7.35 (m, 1 H), 8.0 (m, 1 H), 8.9 (m, 1 H). ^{13}C NMR ($CDCl_3$): 13.7, 17.0, 26.0, 26.2, 26.4, 28.3, 29.5, 32.8, 33.5, 33.9, 39.9, 40.2, 48.2, 53.7, 78.3, 80.1, 135.0, 155.5, 171.6, 210.4. Anal. Calcd for $C_{24}H_{41}ClN_4O_5 \cdot 0.8H_2O$: C, 55.92; H, 8.33; N, 10.87, Cl, 6.88. Found: C, 56.18; H, 8.08; N, 10.71; Cl, 7.07.

(*R)-*N*-[1-(Cyclohexylmethyl)-2,3-dioxohexyl]-*N*²-[(1,1-dimethylethoxy)carbonyl]-1-[(4-methylphenyl)sulfonyl]-L-histidinamide (50).** The Dess–Martin periodinane reagent (308.5 mg, 0.728 equiv) was added to a solution of hydroxy ketone **48** (300 mg, 0.485 mmol) and tBuOH (53.4 mg, 0.728 equiv) in dichloromethane (5 mL). After 2 h, the reaction mixture was diluted with dichloromethane (20 mL) and washed with aqueous $NaHCO_3/Na_2S_2O_3$ (15 mL, 500 mg of $Na_2S_2O_3$ dissolved in 30 mL of saturated $NaHCO_3$) to remove the excess reagent. Drying and concentration gave a residue which was purified by flash chromatography, eluting with 1:1 hexane/ethyl acetate, to yield **50** (288 mg, 96%). Mp: 60–67 °C. TLC: R_f = 0.71 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). $[\alpha]_D$ = −21.6° (*c* = 0.44, MeOH). MS: $(M + H)^+$ 617. ^1H NMR ($CDCl_3$): 0.95 (t, 3 H, *J* = 7), 1.48 (s, 9 H), 0.8–2.0 (m, 15 H), 2.45 (s, 3 H), 2.73 (t, 2 H, *J* = 7), 2.9 (m, 2 H), 4.4 (m, 1 H), 4.95 (m, 1 H), 5.88 (d, 1 H, *J* = 7), 7.12 (s, 1 H), 7.37 (d, 2 H, *J* = 8), 7.83 (d, 2 H, *J* = 8), 7.95 (s, 1 H). ^{13}C NMR ($CDCl_3$): 13.5, 16.2, 21.5, 25.7, 25.9, 26.1, 27.8, 28.1, 30.0, 32.0, 33.6, 34.1, 38.0, 38.2, 51.6, 53.3, 80.1, 114.8, 127.3, 130.3, 134.7, 136.0, 140.4, 146.2, 155.4, 171.1, 197.0, 199.1.

(*R)-*N*-[1-(Cyclohexylmethyl)-2,3-dioxohexyl]-*N*²-[(1,1-dimethylethoxy)carbonyl]-L-histidinamide (51).** HOBt (144 mg, 0.936 mmol) was added in one portion to a solution of the diketone **45** (144 mg, 0.234 mmol) in methanol (10 mL). After 3 h at room temperature, the solvents were removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 19:1:0.05 $CHCl_3$/MeOH/NH_4OH, to provide **51** (90 mg, 83%). TLC: R_f = 0.20 (9:1:0.05 $CHCl_3$/MeOH/NH_4OH). MS: $(M + H)^+$ 463. ^1H NMR ($CDCl_3$, 270 MHz): 0.97 (t, 3 H, *J* = 7), 1.46 (s, 9 H), 0.8–1.9 (m, 15 H), 2.73 (t, 2 H, *J* = 7), 2.9–3.25 (m, 2 H), 4.4 (m, 1 H), 5.0 (m, 1 H), 5.75 (m, 1 H), 7.38 (s, 1 H), 7.6 (s, 1 H).

References

(1) Petrillo, E. W., Jr.; Ondetti, M. A. Angiotensin-Converting Enzyme Inhibitors: Medicinal Chemistry and Biological Actions. *Med. Res. Rev.* **1982**, *2*, 1–38.

(2) For a review of early work on renin inhibitors, see: Greenlee, W. J. Renin Inhibitors. *Med. Res. Rev.* **1990**, *10*, 173–226. For examples of recent research, see: (a) Thaisrivongs, S.; Blinn, J. R.; Pals, D. T.; Turner, S. R. Conformationally Constrained Renin Inhibitory Peptides: Cyclic (3-1)-1-(Carboxymethyl)-L-prolyl-L-phenylalanyl-L-histidinamide as a Conformational Restriction at the P_2-P_4 Tripeptide Portion of the Angiotensinogen Template. *J. Med. Chem.* **1991**, *34*, 1276–1282. (b) Ashton, W. T.; Cantone, C. L.; Tolman, R. L.; Greenlee, W. J.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. Inhibitors of Human Renin with C-Termini Derived from Amides and Esters of α-Mercaptoalkanoic Acids. *J. Med. Chem.* **1992**, *35*, 2772–2781. (c) Doherty, A. M.; Sircar, I.; Kornberg, B. E.; Quin, J., III; Winters, R. T.; Kaltenbronn, J. S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; Ryan, M. J.; Painchaud, C. A. Design and Synthesis of Potent, Selective, and Orally Active Fluorine-Containing Renin Inhibitors. *J. Med. Chem.* **1992**, *35*, 2–14. (d) Kleinert, H. D.; Rosenberg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Dennisen, J. Discovery of a Peptide-Based Renin Inhibitor with Oral Bioavailability and Efficacy. *Science* **1992**, *257*, 1940–1943.

(3) Barrett, A. J.; Salvesen, G. Eds. *Proteinase Inhibitors*; Research monographs in cell and tissue physiology; Dingle, J. T., Gordon, J. L., General Eds.; Elsevier Science Publishers: Amsterdam, The Netherlands, 1986.

(4) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. Fluoro Ketone Inhibitors of Hydrolytic Enzymes. *Biochemistry* **1985**, *24*, 1813–1817.

(5) Kokubu, T.; Hiwada, K.; Nagae, E.; Murakami, E.; Morisawa, Y.; Yabe, Y.; Koike, H.; Iijima, Y. Statine-Containing Dipeptide and Tripeptide Inhibitors of Human Renin. *Hypertension*, **1986**, *8* (suppl II), II-1-II-5.

(6) Bolis, G.; Fung, A. K. L.; Greer, J.; Kleinert, H. D.; Marcotte, P. A.; Perun, T. J.; Plattner, J. J.; Stein, H. H. Renin Inhibitors. Dipeptide Analogues of Angiotensinogen Incorporating Transition-State, Nonpeptidic Replacements at the Scissile Bond. *J. Med. Chem.* **1987**, *30*, 1729–1737.

(7) Kempf, D. J.; Lara, E.; Stein, H. H.; Cohen, J.; Plattner, J. J. Renin Inhibitors Based on Novel Dipeptide Analogues. Incorporation of the Dehydrohydroxyethylene Isostere at the Scissile Bond. *J. Med. Chem.* **1987**, *30*, 1978–1983.

(8) Dellaria, J. F.; Maki, R. G.; Bopp, B. A.; Cohen, J.; Kleinert, H. D.; Luly, J. R.; Merits, I.; Plattner, J. J.; Stein, H. H. Optimization and In Vivo Evaluations of a Series of Small, Potent, and Specific Renin Inhibitors Containing a Novel Leu-Val Replacement. *J. Med. Chem.* **1987**, *30*, 2137–2144.

(9) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; Lamont, B.; Lin, T. Y.; Kawai, M.; Rich, D. H.; Veber, D. F. Renin Inhibitors. Syntheses of Subnanomolar, Competitive, Transition-State Analogue Inhibitors Containing a Novel Analogue of Statine. *J. Med. Chem.* **1985**, *28*, 1779–1790.

(10) The Weinreb amide 1 is extremely stable and can be safely stored at room temperature. The procedure for preparing aldehyde 2 via the stable Weinreb amide was developed by Dr. Harold Weller. For similar synthesis of various α-amino aldehydes, see: (a) Fehrentz, J.-A.; Castro, B. An Efficient Synthesis of Optically Active-α-(*t*-Butoxycarbonylamino)-aldehydes from α-Amino Acids. *Synthesis* **1983**, 676–678. (b) Saari, W. S.; Fisher, T. E. A Convenient and Versatile Synthesis of Chiral Aliphatic and Allylic Amines. *Synthesis* **1990**, 453–454.

(11) For alternate preparations of α-amino aldehyde 2, see ref 9 and the following: (a) Bock, M. G.; Dipardo, R. M.; Evans, B. E.; Freidinger, R. M.; Rittle, K. E.; Payne, L. S.; Boger, J.; Whitter, W. L.; LaMont, B. I.; Ulm, E. H.; Blaine, E. H.; Schorn, T. W.; Veber, D. F. Renin Inhibitors Containing Hydrophilic Groups. Tetrapeptides with Enhanced Aqueous Solubility and Nanomolar Potency. *J. Med. Chem.* **1988**, *31*, 1918–1923. (b) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. A Synthesis of Protected Aminoalkyl Epoxides from α-Amino Acids. *J. Org. Chem.* **1987**, *52*, 1487–1492.

(12) For preparation of configurationaly stable N-protected α-amino aldehydes, see: Lubell, W. D.; Rapoport, H. Configurational Stability of N-Protected α-Amino Aldehydes. *J. Am. Chem. Soc.* **1987**, *109*, 236–239.

(13) For a preliminary communication on the preparation of fluoro ketone 11, see: Patel, D. V.; Rielly-Gauvin, K.; Ryono, Denis, E. Peptidic Trifluoromethyl Alcohols and Ketones. A General Synthesis and Application as Renin Inhibitors. *Tetrahedron Lett.* **1988**, *29*, 4665–4668.

(14) Imperiali, B.; Abeles, R. H. A Versatile Synthesis of Peptidyl Fluoromethyl Ketones. *Tetrahedron Lett.* **1986**, *27*, 135–138.

(15) Bergeson, S. H.; Edwards, P. D.; Krell, R. D.; Shaw, A.; Stein, R. L.; Stein, M. M.; Strimpler, A. M.; Trainor, D. A.; Wildonger, R. A.; Wolanin, D. J. Inhibition of Human Leukocyte Elastase by Peptide Trifluoromethyl Ketones. In *Abstracts of Papers*; 193rd National Meeting of the American Chemical Society, Denver, Colorado, April 5–10, 1987; American Chemical Society: Washington DC, 1987; MEDI 0001.

(16) Hooper, D. G.; Loucks, L. F.; Liu, M. T. H. Preparation of CF_3CHO. *J. Chem. Educ.* **1975**, *52*, 131.

(17) Shioiri, T.; Ninomiya, K.; Yamada, S-I. Diphenylphosphoryl Azide. A New Convenient Reagent for a Modified Curtius Reaction and for the Peptide Synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.

(18) Initially, we only removed the Cbz group from 10 and coupled the TBS protected intermediate directly with the acid 6. However, we were not able to remove the TBS group cleanly from the silyl derivative of tripeptide 12.

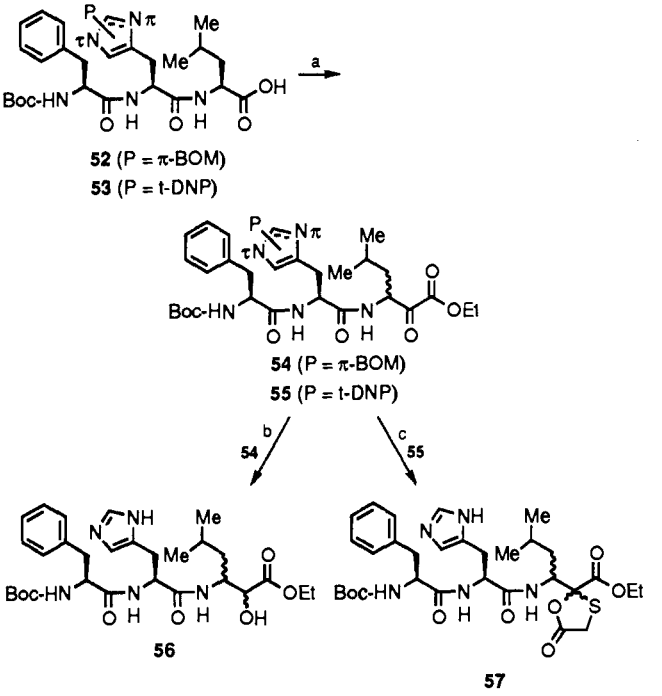
(19) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5[1] Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(20) Dess–Martin oxidation is one of the best methods available for oxidation of alcohols bearing electron-deficient groups to the corresponding activated ketones. For the first application of this reagent toward the preparation of trifluoromethyl ketones, see: (a) Linderman, R. J.; Graves, D. M. An Efficient Procedure for the Oxidation of Fluorinated Carbinols. *Tetrahedron Lett.* **1987**, *28*, 4259–4262. For a detailed account, see: (b) Linderman, R. J.; Graves, D. M. Oxidation of Fluoroalkyl-Substituted Carbinols by the Dess–Martin Reagent. *J. Org. Chem.* **1989**, *54*, 661–668.

(21) Charles, I.; Latham, D. W. S.; Hartley, D.; Oxford, A. W.; Scopes, D. I. C. Bicyclic Heterocycles with Nitrogen at the Ring Junction. Part 2. Application of the Dakin–West Reaction to the Synthesis of Imidazo-[5,1-*f*]-1,2,4-[triazin-4(3*H*)-ones. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1139–1146.

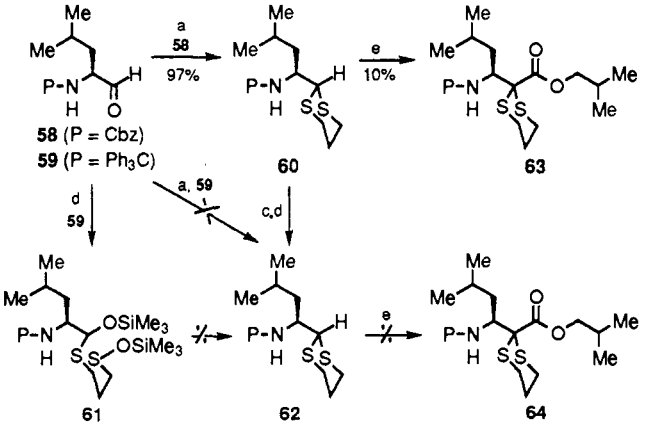
(22) For one of the first applications of peptidic α-keto esters as protease inhibitors, see: Hori, H.; Yasutake, A.; Minematsu, Y.; Powers, J. C. Inhibition of Human Leukocyte Elastase, Porcine Pancreatic Elastase and Cathepsin G by Peptide Ketones. In *Peptides Structure and Function*; Proceedings of the Ninth American Peptide Symposium; Deber, C. M., Hruby, V. J., Kopple, K. D., Eds.; 1985; pp 819–822.

(23) Although the modified Dakin–West procedure worked reasonably well for protected histidine bearing peptides 52 and 53, difficulties were encountered during the final deprotection steps. Attempted removal of the BOM group from 54 resulted in simultaneous reduction of the α-keto ester functionality to afford the hydroxy ester 56. Removal of the 2,4-dinitrophenyl (DNP) group from 55 with mercaptoacetic acid also failed to afford the desired product and alternatively gave the thioketal type intermediate 57.



Reagents: (a) $ClC(O)CO_2Et$, pyridine, DMAP; (b) H_2, $Pd(OH)_2$/C; (c) $HSCH_2CO_2H$.

(24) Our initial attempts centered on converting a suitably protected α-amino aldehyde into a dithiane and then acylating it with an alkyl chloroformate. Thus, *N*-Cbz-L-Leucinal (58) was efficiently converted to the dithiane 60, but acylation of 60 under various reaction conditions gave only modest yields of the desired ester 63. Alternatively, we decided to investigate this chemistry utilizing the *N*-trityl group. As expected, preparation of 62 directly from *N*-trityl-L-leucinal (59) using BF_3-Et_2O was unsuccessful. Attempted conversion under neutral conditions gave 61 as the only isolable intermediate, which could not be converted to 62. The trityl-protected dithiane intermediate 62 was eventually prepared from 60 by hydrogenolysis followed by N-tritylation. Unfortunately, acylation of the dithiane 62 to 64 was unsuccessful under a variety of conditions.



Reagents: (a) BF_3-Et_2O, $HS(CH_2)_2SH$; (b) ZnI_2, $Me_3SiS(CH_2)_2SSiMe_3$; (c) Me_3Si, (d) Ph_3CCl, iPr_2NEt; (e) nBuLi, $ClCO_2iBu$.

(25) Application of α-hydroxy ester based peptides as renin inhibitors was reported right after our own work was completed. See: (a) Iizuka, K.; Kamijo, T.; Kubota, T.; Akahane, K.; Umeyama, H.; Kiso, Y. New Human Renin Inhibitors Containing an Unnatural Amino Acid, Norstatine. *J. Med. Chem.* **1988**, *31*, 701–704. (b) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. Orally Potent Human Renin Inhibitors Derived from Angiotensinogen Transition State: Design, Synthesis, and Mode of Interaction. *J. Med. Chem.* **1990**, *33*, 2707–2714.

(26) (a) Seebach, D. Metalated Orthothioformates. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 442–443. (b) Damon, R. E.; Luo, T.; Schlessinger, R. H. A General Synthesis of 2-Alkyl Tetronic Acids. *Tetrahedron Lett.* **1976**, *32*, 2749–2752. (c) D. Seebach. *Chem. Ber.* **1972**, *105*, 487–510.

(27) (a) Ellison, R. A.; Woessner, W. D.; Williams, C. C. New Synthetic Methods from Dithianes. A Convenient Oxidation of Aldehydes to Acids and Esters. *J. Org. Chem.* **1972**, *37*, 2757–2759. (b) Ellison, R. A.; Woessner, W. D.; Williams, C. C. Hydrolysis and Alcoholysis of Orthothio Esters. *J. Org. Chem.* **1974**, *39*, 1430–1433. (c) Dailey, O. D., Jr.; Fuchs, P. L. Synthesis of a Model for the BCE Ring System of Bruceantin. A Caveat on the Cyclohexene -> Trans Diaxial Diol Conversion. *J. Org. Chem.* **1980**, *45*, 216–236. (d) Hengeveld, J. E.; Grief, V.; Tadanier, J.; Lee, C.-M.; Riley, D.; Lartey, P. A. A General Synthesis of Methyl Aldulosonates Using Tris-(Methylthio) Methyl Lithium as the Ester Anion Equivalent. *Tetrahedron Lett.* **1984**, *25*, 4075–4078.

(28) A very similar structural correlation was recently reported in ref 25b.

(29) (a) Rich, D. H.; Sun, E. T. O.; Ulm, E. Synthesis of Analogues of the Carboxyl Protease Inhibitor Pepstatin. Effect of Structure on Inhibition of Pepsin and Renin. *J. Med. Chem.* **1980**, *23*, 27–33. (b) Defour, M.; Jouin, P.; Poncet, J.; Pantalino, A.; Castro, B. Synthesis and Reduction of α-Amino Ketones Derived from Leucine. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1895–1899.

(30) Cardillo, G.; Orena, M.; Sandri, S.; Tamasini, C. Synthesis of Oxazolidin-2-ones Using Carbonate Ion on a Polymeric Support. *Tetrahedron* **1985**, *41*, 163–167.

(31) For preparation of **29** , see: Weller, H, N, III; Ryono, D. E. US Patent 5,055,466. For a similar preparation of the napthyl derivative of this phenyalanine analog, see: Harada, H.; Yamaguchi, T.; Iyobe, A.; Tsubaki, A.; Kamijo, T.; Iizuka, K.; Ogira, K.; Kiso, Y. A Practical Synthesis of the (2*R*)-3-(Morpholinocarbonyl)-2-(1-naphthylmethyl)propionyl]-L-histidine Moiety (P_4-P_2) in Renin Inhibitors. *J. Org. Chem.* **1990**, *55*, 1679–1682.

(32) A very similar route for preparing peptidyl α-keto esters was reported in the literature after the completion of our own work. See: Burkhart, J. P.; Peet, N. P.; Bey, P. A Novel Method for the Preparation of Peptidyl α-Keto Esters. *Tetrahedron Lett.* **1990**, *31*, 1385–1388. Their synthesis also lead to an epimeric mixture of α-keto esters; however, racemization in their case was claimed to occur directly during swern oxidation of the chiral α-hydroxy ester intermediate.

(33) Salamone, S. J.; Jordan, F. Synthesis of 9-(3,4-Dioxopentyl)hypoxanthine, the First Arginine-Directed Purine Derivative: An Irreversible Inactivator for Purine Nucleoside Phosphorylase. *Biochemistry* **1982**, *21*, 6383–6388.

(34) Angelastro, M. R.; Peet, N. P.; Bey, P. An Efficient Synthesis of Novel α-Diketone and α-Keto Ester Derivatives of N-Protected Amino Acids and Peptides. *J. Org. Chem.* **1989**, *54*, 3913–3916.

(35) Seebach, D.; Corey, E. J. Generation and Synthetic Applications of 2-Lithio-1,3-dithianes. *J. Org. Chem.* **1975**, *40*, 231–237.

(36) Seebach, D.; Welka, E-M. Alkylation of 2-Lithio-1,3-dithianes with Arenesulfonates of Primary Alcohols. *Synthesis* **1976**, 476–477.

(37) For a review of stereoselective synthesis of β-amino alcohols from α-amino aldehydes, see: Jurczak, J.; Golebiowski, A. Optically Active N-Protected α-Amino Aldehydes in Organic Synthesis. *Chem. Rev.* **1989**, *89*, 149–164. Also see: Reetz, M. T.; Drewes, M. W.; Schmitz, A. Stereoselective Synthesis of β-Amino Alcohols from Optically Active α-Amino Acids. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141–1143.

(38) (a) Ho, T.-L.; Ho, H. C.; Wong, C. M. Dethioacetalisation with Ceric Ammonium Nitrate. *J. Chem. Soc., Chem. Comm.* **1972**, 791. (b) Ho, T.-K. Ceric Ion Oxidation in Organic Chemistry. *Synthesis* **1973**, 347–354. (c) Cristau, H.-J.; Chabaud, B.; Labaudiniere, R.; Christol, H. Removal of Thioacetal Protecting Groups by Cerium (IV) Ammonium Nitrate - Hydrolysis of 1,3-Dithiannes. *Synth. Commun.* **1981**, *11*, 423–428.

(39) Fujita, E.; Nagao, Y.; Kaneko, K. Useful Dethioacetalization with Soft Acid Metal Salts: Thallium Trinitrate and Mercuric Perchlorate. *Chem. Pharm. Bull.* **1978**, *26*, 3743–3751.

(40) (a) Sakakibara, S.; Fujii, T. Synthesis and Use of N^{Im}-Tosyl-L-histidine. *Bull. Chem. Soc.* **1969**, *42*, 1466. (b) Fujii, T.; Sakakibara, S. Studies on the Synthesis of Histidine Peptides. 1. N^{Im}-Tosylhistidine Derivatives as Starting Materials. *Bull. Chem. Soc.* **1974**, *47*, 3146–3151.

(41) Yamada, S.; Kasai, Y.; Shioiri, T. Diethylphosphoryl Cyanide. A New Reagent for the Synthesis of Amides. *Tetrahedron Lett.* **1973**, *14*, 1595–1598.

(42) Sham, H. L.; Stein, H.; Rempel, C. A.; Cohen, J.; Plattner, J. B. Highly potent and specific inhibitors of human renin. *FEBS Lett.* **1987**, *220*, 299–301.

(43) Thaisrivong, S.; Pals, D. T.; Kati, W. M.; Terner, S. R.; Thomasco, L. M. Difluorostatine- and Difluorostatone-Containing Peptides as Potent and Specific Renin Inhibitors. *J. Med. Chem.* **1985**, *28*, 1553–1555.

(44) Thaisrivong, S.; Pals, D. T.; Kati, W. M.; Terner, S. R.; Thomasco, L. M.; Watt, W. Design and Synthesis of Potent and Specific Renin Inhibitors Containing Difluorostatine, Difluorostatone, and Related Analogues. *J. Med. Chem.* **1986**, *29*, 2080–2087.

(45) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. Fluoro Ketone Containing Peptides as Inhibitors of Human Renin. *J. Med. Chem.* **1987**, *30*, 1617–1622.

(46) Tarnus, C.; Jung, M. J.; Remy, J.-M., Baltzer, S.; Schirlin, D. G. New fluoroketones as human renin inhibitors. *FEBS Lett.* **1989**, *249*, 47–50.

(47) Boger, J.; Lohr, N. S.; Ulm, E. H.; Poe, M.; Blaine, E. H.; Fanelli, G. M.; Lin, T.-Y.; Payne, L. S.; Schorn, T. W.; Lamont, B. I.; Vassil, T. C.; Stabilito, I. I.; Veber, D. F.; Rich, D. H.; Bopari, A. S. Novel renin inhibitors containing the amino acid statine. *Nature (London)* **1983**, *303*, 81–84.

(48) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. α-Diketone and α-Keto Ester Derivatives of N-Protected Amino Acids and Peptides as Novel Inhibitors of Cysteine and Serine Proteinases. *J. Med. Chem.* **1990**, *33*, 11–13.