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An Ester Enolate–Claisen Rearrangement Route to Substituted 4-Alkylideneprolines. Studies toward a Definitive Structural Revision of Lucentamycin A

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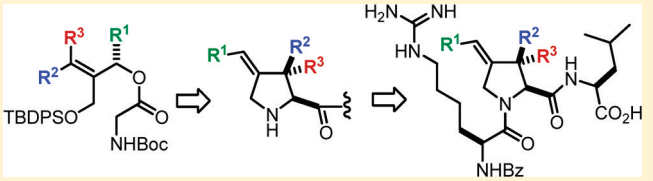
Supporting Information

ABSTRACT: Substituted 4-alkylideneprolines represent a rare class of naturally occurring amino acids with promising biological activities. Lucentamycin A is a cytotoxic, marine-derived tripeptide that harbors a 4-ethylidine-3-methylproline (Emp) residue unique among known peptide natural products. In this paper, we examine the synthesis of Emp and related 4-alkylideneprolines employing a versatile ester enolate–Claisen rearrangement. The scope and selectivity of the key rearrangement reaction are described with a number of diversely substituted glycine ester substrates. Treatment of the allyl esters with excess NaHMDS at ambient temperature gives rise to highly substituted α-allylglycine products with good to excellent diastereoselectivities. Resolution of dipeptide diastereomers and cyclization to form the pyrrolidine rings provide rapid access to stereopure prolyl dipeptides. We have applied this strategy to the synthesis of four Emp-containing isomers of lucentamycin A in pursuit of a definitive stereochemical revision of the natural product. Our studies indicate that the Emp stereogenic centers are not the source of structural misassignment. The current strategy should find broad utility in the synthesis of additional natural product analogues and related 3-alkyl-4-alkylidene prolines.



INTRODUCTION

Chimeric proline residues have long been used in the elucidation of peptide structure–activity relationships.[1] This is due to their influence on the local conformation, recognition, and biological activity of host peptidomimetics. Moreover, a number of alkyl-substituted proline derivatives are present in bioactive natural products,[2] making their chemical synthesis a key component in the discovery of new therapeutic leads.

In 2007, a new family of nonribosomal peptides, lucentamycins A–D, was isolated from the fermentation broth of *Nocardiopsis lucentensis*.[3] Structure elucidation based on NMR and degradation studies revealed unique tripeptides comprised of an N-acylated homoarginine (Har), a C-terminal leucine or tryptophan, and a central 4-ethylidene-3-methylproline (Emp) residue unprecedented in the natural product literature (Figure 1). Of the four closely related structures, lucentamycin A showed potent in vitro growth inhibition of HCT-116 human colon carcinoma cells (IC_{50} = 0.20 μM). The biological activity and structural novelty of lucentamycin A, coupled with our interest in substituted proline derivatives,[4] prompted our group to pursue its synthesis in the hopes of delivering sufficient material for more comprehensive evaluation. In addition, the development of a versatile synthetic strategy toward analogues of **1** became central to a planned structure–activity relationship campaign.

The main challenge in synthesizing members of the lucentamycin family lies in the Emp residue, which is reminiscent of other complex polyalkylprolines such as kainic acid[5] and

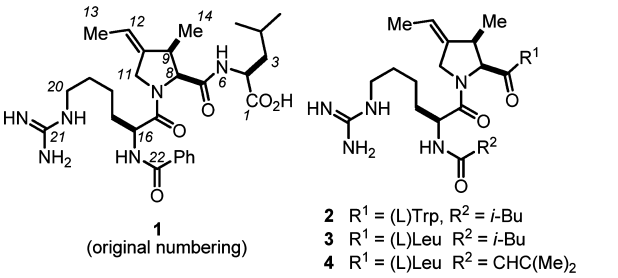


Figure 1. Originally proposed structures of lucentamycins A–D (**1**–**4**, respectively).

A-315675.[6] While 3-methylprolines are relatively common in nature,[2b] 4-alkylideneproline derivatives are exceedingly rare and have been encountered in only a few natural products, including isodomoic acids G and H,[7] tomaymycin,[8] and the recently isolated cytotoxic alkaloid eleganine A (Figure 2).[9] The contiguous pyrrolidine substituents in Emp, their stereochemical relationship, and the C4 alkene geometry complicate retrosynthetic disconnections. For example, selection of 4-oxoproline as a logical precursor leads to a host of potential problems with regard to the relative stereochemistry and regioselectivity of proline alkylation.[10] Proposed biosyntheses for Emp (via selective isoleucine oxidation or complex enzymatic manipulations of L-DOPA)[3] also fail to suggest a

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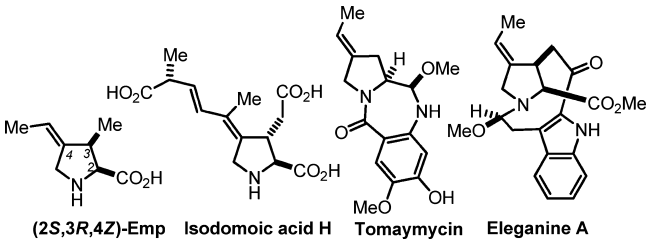
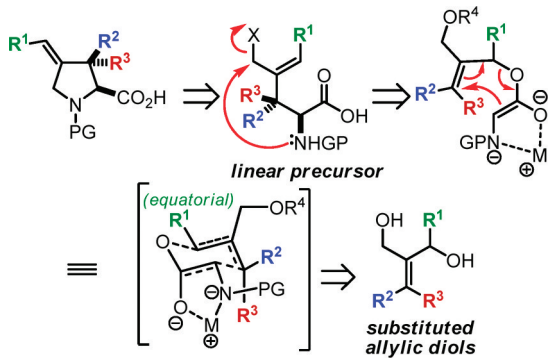


Figure 2. Emp and other naturally occurring 4-alkylideneproline derivatives.

practical synthetic solution. Notably, a derivative of Emp was prepared previously by Gais and co-workers as part of a study on the synthetic utility of chiral vinyl aminosulfoxonium salts.[11] Although intriguing because of the fact that the Emp residue was unprecendented in nature, the described route is not readily amenable to the preparation of other isomers.

We recently reported the synthesis of Emp and the putative structure of lucentamycin A (**1**) relying on the ester enolate–Claisen rearrangement strategy depicted in Scheme 1.[12]

Scheme 1. An Ester Enolate–Claisen Route to 3-Alkyl-4-alkylideneprolines



The key reaction presumably proceeds through a stereoselective chairlike transition state[13] to give the linear proline precursor, setting both stereocenters and the pendant alkene geometry in a single step. We anticipated that varying the R groups on the glycine ester substrate would provide access to other lucentamycin diastereomers as well as an array of complex proline residues, depending on the availability of substituted allylic diol precursors.

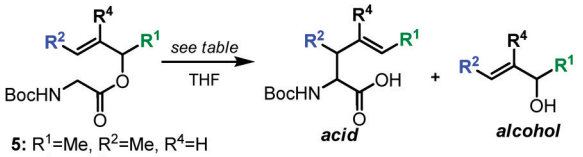
Here, we present an exploration into the scope and stereoselectivity of the key reaction in the context of 4-alkylideneproline synthesis. The ester enolate–Claisen rearrangement route to substituted allylglycines is amenable to the preparation of various complex proline derivatives with moderate to high diastereoselectivities. Application of this strategy to the total synthesis of four lucentamycin A isomers revealed that the structure of the natural product requires revision, and that the Emp stereogenic centers are not the loci of structural misassignment.

RESULTS AND DISCUSSION

Optimization, Scope, and Selectivity of the Enolate–Claisen Rearrangement. Our plan to initiate an SAR campaign around lucentamycin A required both confirmation of its structure and access to analogues. We were particularly interested in evaluating the utility of the enolate–Claisen rearrangement described above in the synthesis of diversely substituted variants. At the outset, it was apparent that a protected hydroxymethyl substituent on the alkene substrate would be required for eventual pyrrolidine ring formation. However, during our synthesis of **1**, we encountered unexpected difficulties in promoting the key reaction under the typical glycine ester enolate–Claisen conditions described by Bartlett[14] and Kazmaier.[15]

We screened various reaction conditions using different model substrates to assess the impact of alkene substitution on product yield (Table 1). In agreement with precedent, we

Table 1. Screening of Ester Enolate–Claisen Rearrangement Conditions



5: R^1=Me, R^2=Me, R^4=H
6: R^1=H, R^2=H, R^4=$CH_2OTBDPS$
7: R^1=Me, R^2=Me, R^4=$CH_2OTBDPS$

entry	ester	conditions[a]	acid yield[b]	alcohol yield[b]
1	**5**	3 equiv of LDA, 1.2 equiv of $ZnCl_2$, −78 °C to rt	73	0
2	**5**	3 equiv of NaHMDS, rt	87	0
3	**5**	3 equiv of NaHMDS, −78 °C to rt	95	0
4	**5**	3 equiv of LiHMDS, 1.2 equiv of $ZnCl_2$, −78 °C to rt	48	0
5	**5**	3 equiv of LDA, 3 equiv of TMSCL, −78 °C to rt	85	0
6	**5**	3 equiv of KHMDS, 0 °C to rt	83	0
7	**6**	3 equiv of LDA, 1.2 equiv of $ZnCl_2$, −78 °C to rt	0	78
8	**6**	3 equiv of KHMDS, 0 °C to rt	14	60
9	**6**	3 equiv of NaHMDS, −78 °C to rt	10	56
10	**6**	1.1 equiv of NaHMDS, rt	0	94
11	**6**	2.5 equiv of NaHMDS, rt	74	23
12	(*S*)-**7**	3 equiv of LDA, 1.2 equiv of $ZnCl_2$, −78 °C to rt	0	69
13	(*S*)-**7**	2.5 equiv of NaHMDS, −78 °C to rt	9	63
14	(*S*)-**7**	1.1 equiv of NaHMDS, rt	0	97
15	(*S*)-**7**	2.5 equiv of NaHMDS, rt	76	23

[a]Reaction progress was monitored by TLC, and times ranged from 5 min to 18 h. [b]Isolated yields.

found that ester **5**,[15] devoid of the silyloxymethyl substituent, afforded good yields of the Boc-protected amino acid under various conditions. However, ester **6**, lacking the methyl substituents and harboring a silyloxymethyl group, consistently gave poor yields of the desired product along with the alcohol precursor to **6**. While the absence of a Lewis acid additive seemed to improve the yield of the carboxylic acid, reducing the equivalency of the base resulted in near quantitative recovery of the fragmentation product (entry 10). On the basis of pK_a considerations, this result suggests that the *N*-Boc group participates in ester cleavage because this anion is presumably formed first. The ester cleavage pathway may be favored over thermally induced rearrangement at lower temperatures, even when the dianion is formed (>2 equiv of base). Indeed, we found that temperature had a dramatic effect on the product ratio (see entries 9 and 11). Fully elaborated substrate (*S*)-**7**[12]

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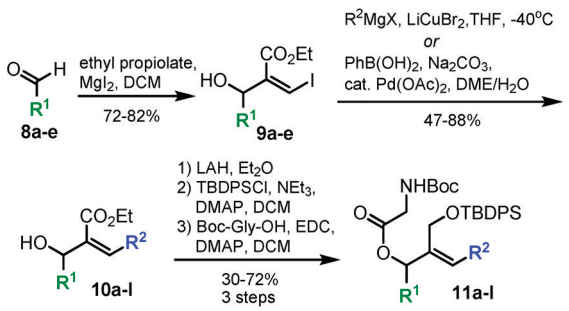
mirrored this trend, confirming that the silyloxymethyl alkene substituent poses an obstacle to the desired pathway. In contrast, the presence of the methyl substituents at R^1 and R^2 had no effect on the product distribution (entries 11 and 15). Under optimized conditions, fragmentation was largely suppressed, resulting in a 76% isolated yield of the desired acid with 99% conversion (entry 15).

We then investigated the effects of other alkene substituents on reaction diastereoselectivity and product distribution. A series of substituted glycine allyl ester derivatives was synthesized as shown in Scheme 2. Iodoacrylates were prepared via

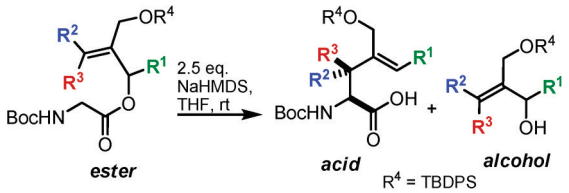
Scheme 2. Synthesis of Diversely Substituted Claisen Rearrangement Substrates



Baylis–Hillman reaction[16] and the alkenes functionalized through either Suzuki or Gilman coupling in good yields.[17] Ester reduction, monosilylation, and condensation with Boc-Gly-OH afforded racemic esters **11a–l**.

The results of enolate–Claisen rearrangement reactions employing 2.5 equiv of NaHMDS are shown in Table 2. After

Table 2. Effects of Substituents on Diastereoselectivity



entry	ester	R^1	R^2	R^3	acid	dr[a]	yield[b]
1	(*S*)-7[12]	Me	Me	H	**12**[12]	>95:5	76 (23)
2	**11a**	Me	*n*-pentyl	H	**13a**	>95:5	77 (18)
3	**11b**	Et	*n*-pentyl	H	**13b**	91:9	60 (10)
4	**11c**	*i*Pr	*n*-pentyl	H	**13c**	90:10	62 (7)
5	**11d**	*t*Bu	*n*-pentyl	H	**13d**	83:17	52 (32)
6	**11e**	Ph	*n*-pentyl	H	**13e**	87:13	74 (9)
7	**11f**	Me	Ph	H	**13f**	>95:5	85 (5)
8	**11g**	Et	Ph	H	**13g**	87:13	76 (11)
9	**11h**	*i*Pr	Ph	H	**13h**	79:21	54 (44)
10	**11i**	*t*Bu	Ph	H	**13i**	78:22	61 (20)
11	**11j**	Ph	Ph	H	**13j**	73:27	69 (18)
12	**11k**	Ph	Me	H	**13k**	>95:5	78 (15)
13	**11l**	Me	Et	H	**131**	>95:5	89 (7)
14	**11m**	H	Me	H	**13m**	>95:5	82 (9)
15	**11n**[c]	H	H	Me	**13n**	94:6	65 (32)

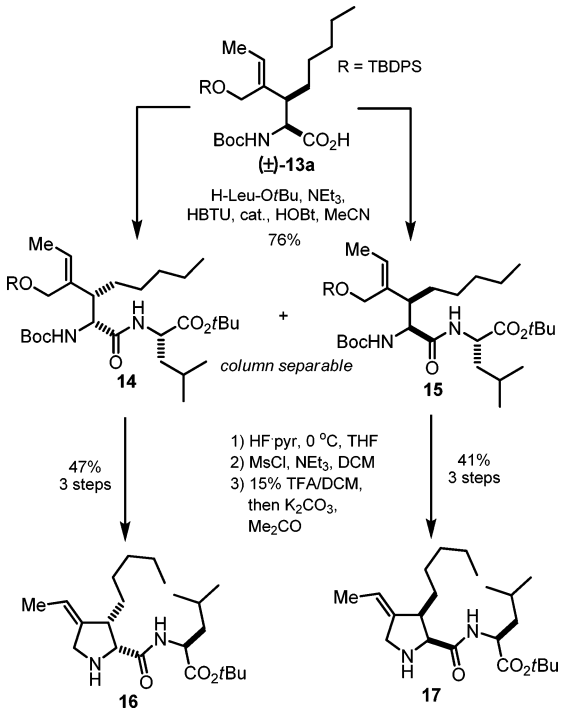
[a]Determined by HPLC of a semicrude product mixture. [b]Combined isolated yield of the diastereomeric mixture (isolated yield of alcohol in parentheses). [c]R_4 = TIPS.

passage through a short silica plug, isolated acids were obtained as diastereomeric mixtures in moderate to high yields. We also attempted to recover any alcohol byproduct during column purification. Combined isolated yields varied from 54 to 89%, with many of the more sterically demanding substrates giving rise to significant amounts of fragmentation byproduct at the expense of the desired acid. Table 2 also lists the isolated yields of the pure recovered alcohol. In some cases (entries 4, 6, and 10), the alcohol coeluted with unidentified impurities artificially suppressing the overall yields. Typically, reaction conversions were greater than 90%.

Although most substrates gave rise to amino acids with good diastereoselectivities, some discernible trends could be identified with respect to steric bulk. Increases in the size of R^1 had a negative impact on dr when R^2 was kept constant (entries 2–5 and 7–10). This result is somewhat counterintuitive on the basis of *A* value considerations and may indicate that large R^1 substituents lead to disruption of an ordered chairlike transition state. Variations in the size of R^2 substituents appeared to have a weaker effect, though some erosion in dr was still observed (compare entries 6, 11, and 12). An allyl ester with a *Z* alkene configuration appeared to be well-tolerated despite a presumed axial disposition in the transition state (entry 15). Only the reaction of esters **11h–j**, featuring two bulky substituents, resulted in diastereomeric ratios of <4:1.

To demonstrate the utility of racemic allylglycine derivatives in the synthesis of diastereopure 3-alkyl-4-alkylideneproline-containing peptides, we selected some *N*-Boc amino acids for further elaboration (Scheme 3).[18] Crude amino acid **13a** was

Scheme 3. Synthesis of Polysubstituted Prolyl Dipeptides 16 and 17



thus reacted with L-leucine *tert*-butyl ester in the presence of HBTU, triethylamine, and a catalytic amount of HOBt to afford amides **14** and **15** in good yield. The diastereomeric dipeptides could be readily separated by flash column chromatography.

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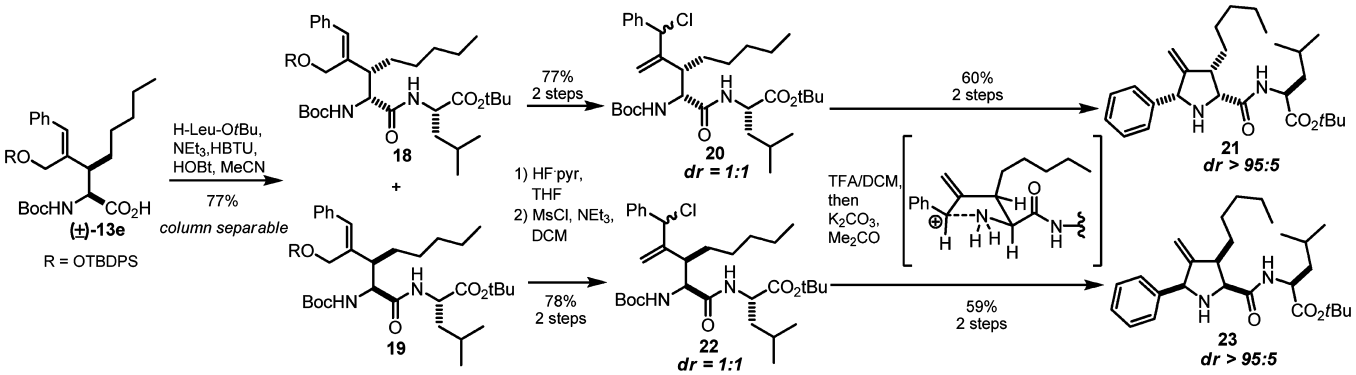
Scheme 4. Proposed Stereoselective S_N1 Ring Closure to Form Phenylprolines 21 and 23



Removal of the silyl protecting groups was followed by activation of the resulting allylic alcohol in the presence of methanesulfonyl chloride and triethylamine. Stirring at room temperature led to exclusive formation of the primary allylic chloride intermediate in high yield.[19] Acidolysis of the Boc group and treatment with potassium carbonate afforded the stereopure prolyl dipeptides **16** and **17** in 47 and 41% overall yield, respectively.

When racemic **13e** was used as a starting material, the corresponding leucyl derivatives could likewise be separated by column (Scheme 4). However, we found that the one-pot mesylation/chlorination procedure gave rise to an equimolar mixture of secondary allylic chlorides. The presence of a terminal alkene in both **20** and **22** was confirmed by DEPT NMR. Remarkably, treatment of each of the diastereomeric mixtures with TFA followed by basification with K_2CO_3 afforded the corresponding 5-phenylproline derivatives (**21** and **23**) as single isomers. One-dimensional NOE studies were used to establish the all-*cis* configuration about the pyrrolidine rings. No other stereo- or regioisomers were detected in the crude reaction mixtures. These results indicate that ring closure occurs through an S_N1 mechanism involving stereoselective attack of the amine onto the incipient carbocation. This pathway appears to be unique to the phenyl (R^1)-substituted substrate as elaboration of alkyl-substituted variants did not give rise to any secondary allylic chlorides or the 5-substituted prolines. The generality of this reaction for the synthesis of other highly substituted 5-arylprolines warrants further investigation.

Application to the Synthesis of Presumed Lucentamycin A and Its Isomers. Our next goal was to apply the methodology described above to the synthesis of Emp diastereomers for incorporation into lucentamycin tripeptides. In our initial synthesis of **1**, we noted differences in NMR chemical shifts between our material and the natural isolate.[12] We have since obtained a crystal structure of the synthetic compound, confirming the need for revision (Figure 3). Lindsley and co-workers subsequently described the synthesis of another unnatural diastereomer of lucentaymcin A as well as the simplified proline-containing analogue, neither of which exhibited activity toward HCT-116 cells.[20] These potential eudismic discrepancies underscored the need for efficient access to each of the Emp diastereomers.

The original structure elucidation of natural lucentamycin A relied on ROESY correlations to establish the *Z* alkene geometry as well as the *cis* relationship between the Emp methine protons on C8 and C9.[3] The absolute configuration of

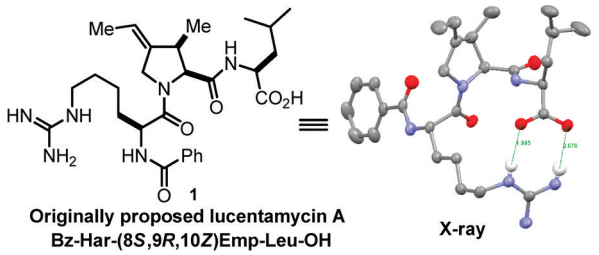


Figure 3. Crystal structure of **1**.

the Emp residue was determined by Marfey derivatization of the acid hydrolysate. Because this assignment relied on an assumption of a typical HPLC elution order for 1-fluoro-2,4-dinitrophenyl-5-L-leucinamide (FDLA) derivatives of known amino acids, we hypothesized that the C8 stereochemistry of the Emp residue may be in need of correction. In addition, molecular models suggested that accessible proline conformations may give rise to H_{C8}–H_{C9} Overhauser correlations, even in the case of a *trans* relationship.

We first prepared Bz-Har-(8*R*,9*S*,10*Z*)-Emp-Leu-OH (**27**) using (+)-methyl lactate as a chiral progenitor (Scheme 5). As expected, the enolate–Claisen rearrangement of (*R*)-**7** proceeded with high enantio- and diastereoselectivity on the basis of HPLC analysis of acid **24** and dipeptide **25**. Formation of the pyrrolidine ring over three steps was followed by condensation with Fmoc-(L)Har(Boc)$_2$-OH, N-terminal group interconversion, and global deprotection. Unfortunately, the ^{1}H NMR spectrum of **27** did not correlate with that of the natural product. In particular, the α-proton at C8 appeared significantly downfield relative to that in lucentamycin A. The protons at C9 and C12, in contrast, were shifted slightly upfield.

Access to the 8,9-*trans* Emp isomers required extension of the Claisen rearrangement to a trisubstituted *Z* alkene substrate. As with **7**, this reaction would presumably proceed through a chairlike transition state but with the terminal methyl group forced to occupy an axial position. We pursued the synthesis of the requisite racemic glycine ester in hopes of again resolving the diastereomeric leucyl derivatives (Scheme 6). Thus, enoate **29** was prepared in multigram quantities following a known procedure.[21] Hydride reduction, selective silyl ether formation, and condensation with Boc-glycine then provided ester **30** in good yield. Treatment of **30** with 2.5 equiv of NaHMDS at room temperature led to the formation of (±)-**31** in 78% yield and >95:5 dr, as judged by HPLC.

As with racemic *N*-Boc amino acids **13a** and **13e**, coupling of **31** to L-leucine *tert*-butyl ester afforded diastereomers **32** and

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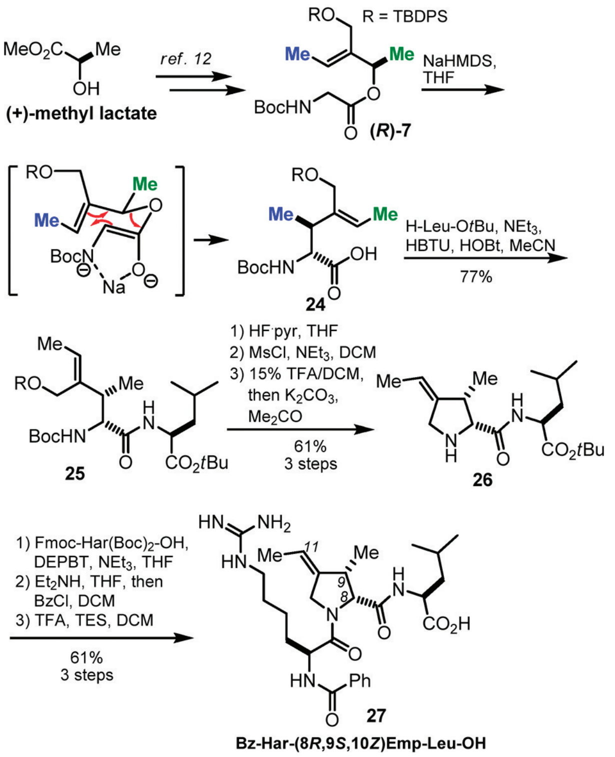
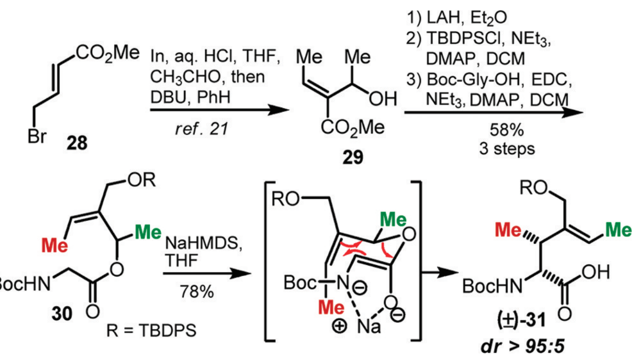
Scheme 5. Synthesis of Bz-Har-(8*R*,9*S*,10*Z*)-Emp-Leu-OH (27)



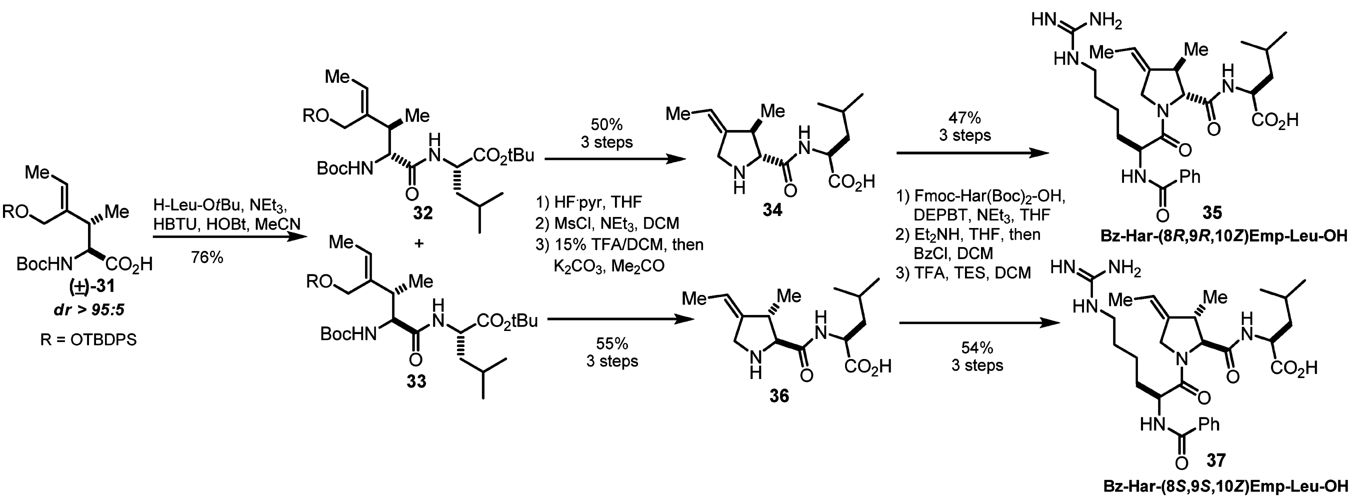
Scheme 6. Toward the *trans* Emp Diastereomers



33, respectively, which could be readily separated by flash column chromatography (Scheme 7). Each of these compounds was cyclized to form intermediates **34** and **36**, respectively, and converted to their corresponding tripeptides according to our previous protocol. Notably, the syntheses of these compounds are considerably shorter than our previous route toward **1** (12 vs 17 steps from commercially available starting materials) primarily because of the rapid and scalable preparation of known enoate **29**. Enantiopure **29** could also be obtained by isomerization of the lactate-derived chiral (*Z*)-enoate[12] in the presence of DBU. However, we have found the route described in Scheme 7 to be more practical for the synthesis of large quantitites of Emp-containing peptides.

Following the purification of **35** and **37** by RP-HPLC, we carried out complete characterization for comparison with the natural product. As expected, the NMR data for one of the tripeptides (**27**) matched those previously reported by Lindsley and co-workers[20] and exhibited significant chemical shift differences relative to those of natural lucentamycin A. We were surprised to find that compound **37** also failed to correspond to the structure of the natural product, indicating that the Emp stereochemical assignments are not solely responsible for the structural misassignment. Examination of the ^{1}H NMR resonances for each compound also revealed some interesting patterns. Figure 4 depicts the deviations in proton chemical shifts for each synthetic isomer relative to natural lucentamycin A. Tripeptides **27** and **35**, which both harbor D-Emp (8*R*) residues, exhibited the largest chemical shift differences, particulary in the Emp region. The effect of the C8 configuration on Har and Leu proton shifts was also quite pronounced, indicating a considerable change in the global conformation. This may be explained in part by the intramolecular head-to-tail salt bridge observed in the X-ray structure of **1** (Figure 3). A change in the stereochemistry at the Emp α-carbon may result in a significant disruption of this macrocyclic conformation. Taken together, our data suggest that the natural Emp residue is most likely 8*S*,9*R*, as originally proposed. Efforts to systematically vary the alkene geometry as well as the Har and Leu configurations are currently underway. Finally, compounds **1**, **27**, **35**, and **37** were evaluated for growth inhibition of HCT-116 cells using a cell titer blue assay but did not exhibit significant activity below 100 μM.

Scheme 7. Expedient Synthesis of Tripeptides 35 and 37



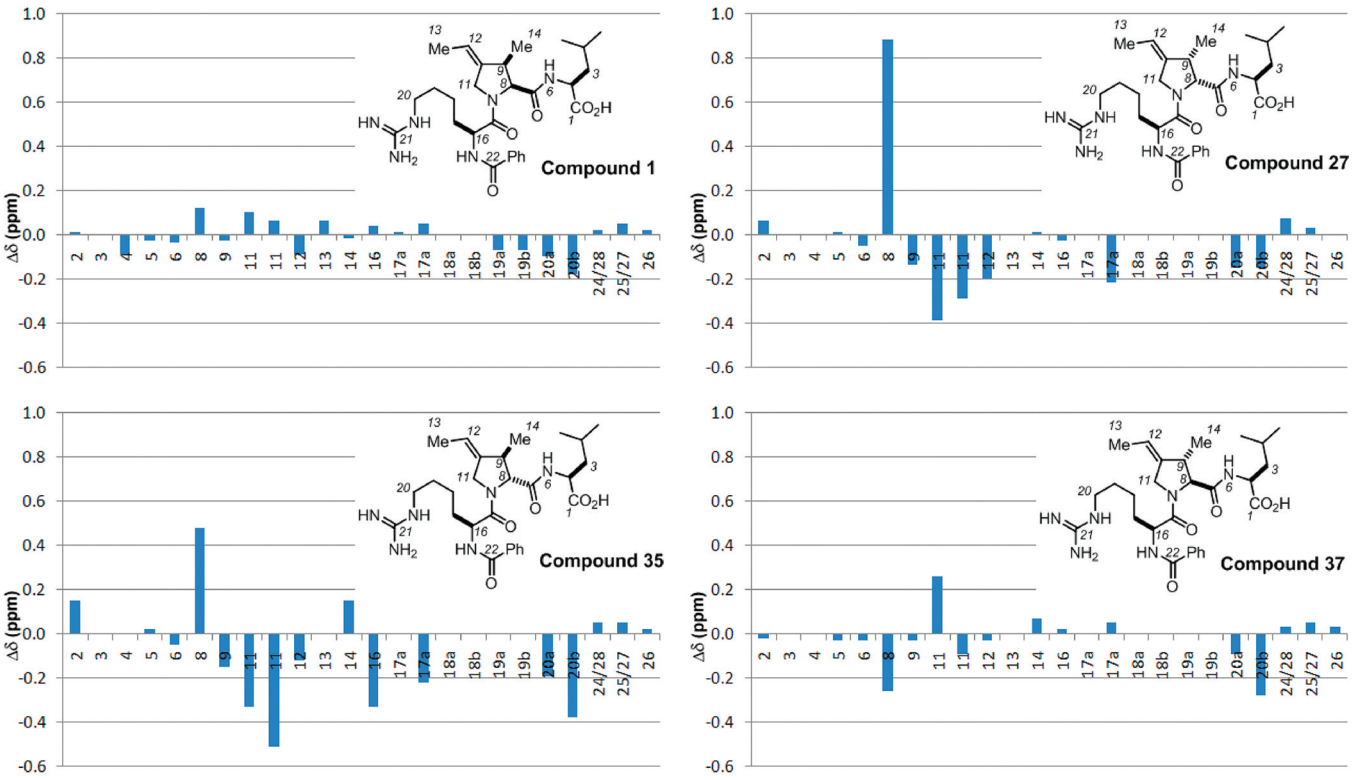


Figure 4. Deviation in nonexchangeable ^{1}H NMR chemical shifts (in DMSO-d_6) for isomers **1**, **27**, **35**, and **37** relative to natural lucentamycin A. The original numbering system was used. Only chemical shift differences for hydrogens on carbons are listed. In cases where proton shifts were within a range, the minimum possible difference is shown.

CONCLUSIONS

We have investigated the scope and selectivity of a NaHMDS-promoted ester enolate−Claisen rearrangement for the synthesis of substituted 4-alkylidene prolines. The key reaction was found to be tolerant of various alkene substituents, resulting in good product yields and diastereomeric ratios in all but the most sterically demanding cases. Selected α-allylglycine products were elaborated into diversely subtituted prolyl dipeptides. We have employed this approach to access each of the possible diastereomers of 4-ethylidene-3-methylproline, the central residue proposed for lucentamycin A. Resolution of diastereomeric dipeptides en route to the final products resulted in a streamlined synthesis of lucentamycin isomers, starting from racemic enolate−Claisen substrates. While the key reaction provides ready access to the target tripeptides, compounds **1**, **27**, **35**, and **37** each exhibit discrepancies with the natural product by NMR. Efforts to exhaust other stereocenters as the source of structural misassignment are ongoing. Given the importance of substituted prolines in bioactive compounds, we anticipate that the described studies will find utility in the synthesis of related natural products and constrained peptidomimetics.

EXPERIMENTAL SECTION

General. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen gas using dry solvents. Commercial grade reagents and solvents were used without further purification except where noted. Diethyl ether, toluene, dimethylformamide dichloromethane, and tetrahydrofuran were purified by solvent purification system. Other anhydrous solvents were purchased directly from chemical suppliers. Thin layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed using silica gel (60 μm particle size). The purity of all compounds was judged by TLC analysis (single spot/two solvent systems) using a UV lamp, CAM (ceric ammonium molybdate), ninhydrin, or basic $KMnO_4$ stain(s) for detection purposes. NMR spectra were recorded on a 400 MHz spectrometer. Mass spectral data were measured with high-resolution ESI-TOF instrument in positive or negative mode. ^{1}H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard. Analytical RP-HPLC was performed on a C_{18} column (4 mm × 150 mm) with an acetonitrile/water (0.1% formic acid) mixture as the eluent (1 mL/min flow rate). Semipreparative RP-HPLC was performed on a C_{18} column (9.4 mm × 250 mm) with an acetonitrile/water (0.1% formic acid) mixture as the eluent (4 mL/min flow rate).

2-[(*tert*-Butyldiphenylsilyloxy)methyl]allyl 2-(*tert*-Butoxycarbonylamino)acetate (6). A solution of 2-[(*tert*-butyldiphenylsilyloxy)methyl]prop-2-en-1-ol[22] (142 mg, 0.435 mmol) in 10 mL of CH_2Cl_2 at rt was treated with Boc-Gly-OH (0.099 g, 0.565 mmol), DMAP (0.027 g, 0.218 mmol), and EDC (108 mg, 565 mmol). The mixture was stirred for 20 h, the reaction quenched with saturated aq NH_4Cl, and the mixture extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded **6** as a thick colorless oil (206 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.41 (m, 1H), 5.33 (m, 1H), 5.18 (m, 1H), 4.95 (bs, 1H), 4.66 (s, 2H), 4.18 (s, 2H), 3.86 (d, J = 5.6 Hz, 2H), 1.44 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 155.8, 142.3, 135.6, 133.4, 129.9, 127.9, 113.9, 80.2, 65.5, 64.5, 42.5, 28.4, 26.9, 19.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{37}NO_5Si$ 484.25138, found 484.25193.

(*Z*)-Ethyl 3-Hydroxy-2-(iodomethylene)butanoate (9a). A flask charged with dry CH_2Cl_2 (10 mL) and MgI (1.33 g, 4.80 mmol) was cooled to 0 °C over an ice bath and treated dropwise with ethyl propiolate (0.49 mL, 4.80 mmol). Acetaldehyde (0.23 mL, 4.00 mmol) was then added dropwise, and the reaction mixture was allowed to warm to rt while being stirred overnight. The reaction was

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quenched with 10% aq $Na_2S_2O_3$ and the mixture stirred vigorously until the layers separated. The phases were separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator for purification by flash chromatography (5−10% EtOAc/hexanes). Pure **9a** was isolated as an orange oil (0.80 g, 74%) in addition to the corresponding *E* isomer (0.13 g, 12%). Data for major *Z* isomer **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 1.1 Hz, 1H), 4.61 (q, J = 6.4 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.31 (bs, 1H), 1.38 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 148.0, 83.7, 70.3, 61.6, 22.4, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_7H_{11}IO_3Na$ 292.9645, found 292.9653.

(*Z*)-Ethyl 3-Hydroxy-2-(iodomethylene)pentanoate (9b). Prepared as described for **9a** using 1-propanal in place of acetaldehyde (72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 1.0, 1H), 4.32 (q, J = 7.1 Hz, 3H), 2.35 (d, J = 6.4 Hz, 1H), 1.75−1.59 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 146.7, 84.4, 76.6, 61.6, 29.2, 14.3, 10.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_8H_{13}IO_3Na$ 306.9802, found 306.9790.

(*Z*)-Ethyl 3-Hydroxy-2-(iodomethylene)-4-methylpentanoate (9c). Prepared as described for **9a** using isobutyraldehyde in place of acetaldehyde (74%). Spectral data matched those previously reported for enantiopure **9c**.[17]

(*Z*)-Ethyl 3-Hydroxy-2-(iodomethylene)-4,4-dimethylpentanoate (9d). Prepared as described for **9a** using pivaldehyde in place of acetaldehyde (82%). Spectral data matched those previously reported for enantiopure **9d**.[23]

(*Z*)-Ethyl 2-[Hydroxy(phenyl)methyl]-3-phenylacrylate (9e). Prepared as described for **9a** using benzaldehyde in place of acetaldehyde (74%). Spectral data matched those previously reported for enantiopure **9e**.[17]

(*Z*)-Ethyl 2-(1-Hydroxyethyl)oct-2-enoate (10a). A flame-dried flask was cooled and purged with argon. LiBr (0.09 g, 1.00 mmol) and CuBr (0.14 g, 1.00 mmol) were added in a single portion and dissolved in dry THF (2 mL). A stir bar was added to a separate round-bottom flask containing **9a** (0.71 g, 2.61 mmol) in dry THF (15 mL), and the contents were cooled to −40 °C and stirred. The $LiCuBr_2$ solution described above (0.5 M in THF, 1.04 mL, 0.522 mmol) was added followed by dropwise addition of pentylmagnesium bromide (2 M solution in Et_2O, 3.92 mL, 7.84 mmol) over 10 min. The reaction mixture was allowed to stir for an additional 20 min and the reaction quenched by dropwise addition of saturated aq. NH_4Cl (**CAUTION: gas evolution**). The mixture was diluted with water and the solution stirred until the aqueous phase turned deep blue (∼10 min). The phases were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator for purification by flash chromatography (5−10% EtOAc/hexane) to afford **10a** as a pale orange oil (0.47 g, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (t, J = 7.5 Hz, 1H), 4.47 (q, J = 6.4 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.41 (m, J = 15.0, 7.5 Hz, 2H), 1.48−1.38 (m, 2H), 1.37−1.23 (m, 11H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 141.8, 135.2, 69.9, 60.6, 31.7, 29.5, 29.1, 22.8, 22.6, 14.4, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{12}H_{22}O_3Na$ 237.1461, found 237.1471.

(*Z*)-Ethyl 2-(1-Hydroxypropyl)oct-2-enoate (10b). Prepared from **9b** as described for the **9a** → **10a** reaction (88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (t, J = 7.5 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.12 (t, J = 6.8 Hz, 1H), 2.42 (m, J = 14.9, 7.5 Hz, 2H), 1.72−1.59 (m, 2H), 1.48−1.38 (m, 2H), 1.31 (m, 8H), 0.90 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 142.9, 133.8, 76.4, 60.6, 31.7, 29.6, 29.5, 29.1, 22.6, 14.4, 14.2, 10.6; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1618, found 251.1633.

(*Z*)-Ethyl 2-(1-Hydroxy-2-methylpropyl)oct-2-enoate (10c). Prepared from **9c** as described for the **9a** → **10a** reaction (75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (t, J = 7.6 Hz, 1H), 4.24 (qd, J = 7.1, 0.8 Hz, 2H), 3.79 (t, J = 8.0 Hz, 1H), 2.64 (dd, J = 17.5, 8.7 Hz, 1H), 2.39 (m, 2H), 1.83 (m, 1H), 1.43 (m, 2H), 1.35−1.26 (m, 7H), 0.98 (m, 3H), 0.89 (m, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 143.5, 133.2, 81.3, 60.6, 33.4, 31.7, 29.6, 29.1, 22.6, 19.8, 18.8, 14.4, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{26}O_3Na$ 265.17742, found 265.17885.

(*Z*)-Ethyl 2-(1-Hydroxy-2,2-dimethylpropyl)oct-2-enoate (10d). Prepared from **9d** as described for the **9a** → **10a** reaction (87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (t, J = 7.6 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.04 (s, 1H), 3.02 (bs, 1H), 2.34 (q, J = 15.0, 7.5 Hz, 2H), 1.48−1.38 (m, 2H), 1.35−1.27 (m, 7H), 0.88 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 142.9, 132.0, 82.3, 60.7, 36.3, 31.7, 29.6, 29.1, 26.1, 22.6, 14.3, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{28}O_3Na$ 279.1931, found 279.1949.

(*Z*)-Ethyl 2-[Hydroxy(phenyl)methyl]oct-2-enoate (10e). Prepared from **9e** as described for the **9a** → **10a** reaction (75%). Spectral data matched those previously reported for enantiopure **10e**.[17]

(*Z*)-Ethyl 2-Benzylidene-3-hydroxybutanoate (10f). A stir bar was added to a round-bottom flask containing **9a** (0.803 g, 2.97 mmol) and a 1:1 dimethoxyethane/H_2O mixture (10 mL). Solid Na_2CO_3 (0.944 g, 8.91 mmol) was added in a single portion to the stirring solution, followed by phenylboronic acid (0.398 g, 3.27 mmol). $Pd(OAc)_2$ (0.067 g, 0.297 mmol) was added in a single portion and the solution stirred overnight at rt. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator for purification by flash chromatography (10% EtOAc/hexanes, flushed with 10% MeOH/EtOAc) to afford **10f** as a colorless oil (0.498 g, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 6.90 (s, 1H), 4.65 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.51 (bs, 1H), 1.47 (d, J = 6.5 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 137.7, 135.6, 132.6, 128.4, 128.3, 128.2, 70.1, 61.1, 22.5, 13.9; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}O_3Na$ 243.0992, found 243.1005.

(*Z*)-Ethyl 2-Benzylidene-3-hydroxypentanoate (10g). Prepared from **9b** as described for the **9a** → **10f** reaction (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 6.86 (s, 1H), 4.32 (t, J = 6.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.80−1.70 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 136.5, 135.6, 133.6, 128.4, 128.3, 128.2, 76.2, 61.1, 29.3, 13.9, 10.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{18}O_3Na$ 257.1148, found 257.1170.

(*Z*)-Ethyl 2-Benzylidene-3-hydroxy-4-methylpentanoate (10h). Prepared from **9c** as described for the **9a** → **10f** reaction (72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 6.83 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.03 (d, J = 7.5 Hz, 1H), 2.48 (bs, 1H), 1.91 (m, 1H), 1.10 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 135.8, 135.6, 134.5, 128.4, 128.3, 128.2, 80.8, 61.1, 33.1, 19.6, 18.3, 13.8; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1305, found 271.1301.

(*Z*)-Ethyl 2-Benzylidene-3-hydroxy-4,4-dimethylpentanoate (10i). Prepared from **9d** as described for the **9a** → **10f** reaction (56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3−7.19 (m, 5H), 6.89 (s, 1H), 4.19 (s, 1H), 2.81 (bs, 1H), 4.11−4.02 (m, 2H), 1.04 (m, J = 7.1, 3.5 Hz, 3H), 0.97 (d, J = 3.5 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 136.4, 136.0, 134.7, 128.3, 128.2, 128.1, 82.5, 61.1, 36.6, 26.0, 13.6; HRMS m/z (ESI-TOF) [M + Na]$^+$ calcd for $C_{16}H_{22}O_3Na$ 285.1461, found 285.1476.

(Z)-Ethyl 2-[Hydroxy(phenyl)methyl]-3-phenylacrylate (10j). Prepared from **9d** as described for the **9a** → **10f** reaction (56%). Spectral data matched those previously reported for enantiopure **10j**.[17]

(*Z*)-Ethyl 2-[Hydroxy(phenyl)methyl]but-2-enoate (10k). Prepared from **9e** as described for the **9a** → **10a** reaction, using methylmagnesium bromide in place of pentylmagnesium bromide (47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 6.31 (q, J = 7.2 Hz, 1H), 5.43 (d, J = 7.0 Hz, 1H), 4.23−4.08 (m, 2H), 3.13 (d, J = 7.1 Hz, 1H), 2.06 (d, J = 7.2 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 142.3, 139.2, 134.7, 128.4, 127.6, 126.4, 75.6, 60.6, 15.7, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}O_3Na$ 243.0992, found 243.0991.

(*Z*)-Ethyl 2-(1-Hydroxyethyl)pent-2-enoate (10l). Prepared from **9b** as described for the **9a** → **10a** reaction, using ethylmagnesium

bromide in place of pentylmagnesium bromide (88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (t, J = 7.4 Hz, 1H), 4.47 (q, J = 6.4 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.43 (m, J = 7.5 Hz, 2H), 1.33 (m, 6H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 142.9, 134.8, 69.7, 60.6, 22.9, 22.7, 14.4, 13.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_9H_{16}O_3Na$ 195.0992, found 195.1010.

(*E*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]non-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate (11a). Allylic alcohol **10a** (472 mg, 10.0 mmol) in 50 mL of Et_2O was cooled to 0 °C and treated with LAH (1 M solution in THF, 2.65 mmol, 2.65 mL). The mixture was stirred from 0 to 10 °C for 1 h and the reaction quenched carefully with saturated aq Rochelle salt. When no more gas evolution was observed, the reaction mixture was diluted with 20 mL each of saturated aq Rochelle salt and Et_2O and stirred vigorously at rt for 20 h. The reaction mixture was diluted with brine and extracted repeatedly with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (EtOAc/hexanes) gave the inetermediate diol as a colorless oil (278 mg, 73%).

The allylic diol mentioned above (475 mg, 2.76 mmol) in 10 mL of CH_2Cl_2 under Ar at 0 °C was treated with DMAP (0.067 g, 0.550 mmol) and NEt_3 (0.461 mL, 3.30 mmol) and TBDPSCl (0.776 mL, 3.03 mmol). The mixture was stirred at rt for 23 h and the reaction quenched with saturated aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and evaporated. The crude residue was absorbed onto silica gel and purified by flash column chromatography (5%−10% EtOAc/hexanes) to afford the silyl ether as a colorless oil (1.040 g, 92%).

A solution of the silyl ether mentioned above (918 mg, 2.24 mmol) in 10 mL of CH_2Cl_2 at rt was treated with Boc-Gly-OH (510 mg, 2.91 mmol), DMAP (137 mg, 1.12 mmol), and EDC (558 mg, 2.91 mmol). The mixture was stirred for 20 h, the reaction quenched with saturated aq NH_4Cl, and the mixture extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded **11a** as a thick colorless oil (1.22 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.7−7.58 (m, 4H), 7.47−7.31 (m, 6H), 5.61 (q, J = 6.5 Hz, 1H), 5.55 (t, J = 7.3 Hz, 1H), 4.97 (m, 1H), 4.25−4.09 (m, 2H), 3.88 (m, 1H), 3.79 (m, 1H), 1.84 (dd, J = 14.9, 7.4 Hz, 2H), 1.43 (m, 11H), 1.30−1.06 (m, 7H), 1.04 (m, J = 2.6 Hz, 9H), 0.86 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 155.9, 137.2, 136.1, 135.90, 135.87, 135.6, 135.1, 133.7, 133.6, 130.6, 130.0, 129.8, 127.94, 127.91, 127.8, 127.7, 80.1, 73.7, 59.6, 42.9, 32.0, 31.7, 29.8, 29.5, 29.3, 28.6, 27.7, 27.6, 27.2, 27.1, 27.0, 26.8, 22.7, 20.2, 19.5, 19.4, 19.3, 14.4, 14.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{50}NO_5Si$ 568.34528, found 568.34500.

(*E*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]dec-4-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11b). Prepared from **10b** using the same three-step procedure described for the **10a** → **11a** reaction (62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 4H), 7.46−7.35 (m, 6H), 5.53 (t, J = 7.3 Hz, 1H), 5.36 (t, J = 6.7 Hz, 1H), 4.95 (m, 1H), 4.17 (m, 2H), 3.89 (d, J = 18.3 Hz, 1H), 3.81 (d, J = 18.3 Hz, 1H), 1.92−1.67 (m, 4H), 1.44 (s, 9H), 1.3 −1.11 (m, 6H), 1.04 (s, 9H), 0.87 (dt, J = 19.9, 7.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 155.7, 135.81, 135.77, 135.5, 133.6, 133.5, 132.1, 129.8, 127.8, 79.4, 59.4, 42.7, 31.6, 29.4, 28.5, 27.5, 26.9, 22.6, 19.3, 14.2, 10.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{52}NO_5Si$ 582.36093, found 582.36179

(*E*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2-methyldec-4-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11c). Prepared from **10c** using the same three-step procedure described for the **10a** → **11a** reaction (69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.47−7.35 (m, 6H), 5.51 (t, J = 7.4 Hz, 1H), 5.16 (d, J = 7.6 Hz, 1H), 4.94 (m, 1H), 4.20 (d, J = 11.8 Hz, 1H), 4.10 (d, J = 11.8 Hz, 1H), 3.87 (m, 1H), 3.82 (m, 1H), 2.10 (m, 1H), 1.90 (q, J = 7.3 Hz, 2H), 1.44 (s, 9H), 1.32−1.11 (m, 6H), 1.04 (s, 9H), 0.93−0.82 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 155.7, 135.9, 135.8, 134.6, 133.6, 133.5, 133.3, 129.8, 129.8, 127.8, 127.8, 83.6, 79.9, 59.3, 42.7, 31.6, 30.6, 29.4, 28.5, 27.6, 26.9, 22.6, 19.7, 19.3, 18.1, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{54}NO_5Si$ 596.37658, found 596.37937.

(*E*)-4-[(*tert*-Butyldiphenylsilyloxy)methyl]-2,2-dimethyldec-4-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11d). Prepared from **10d** using the same three-step procedure described for the **10a** → **11a** reaction (45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.46−7.35 (m, 6H), 5.54 (t, J = 7.3 Hz, 1H), 5.21 (s, 1H), 4.88 (m, 1H), 4.21 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 1.94 (q, J = 7.4 Hz, 2H), 1.44 (s, 9H), 1.33−1.11 (m, 6H), 1.05 (s, 9H), 0.89 (s, 9H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 155.7, 135.9, 134.9, 134.8, 133.62, 133.58, 129.79, 129.82, 127.77, 127.75, 83.5, 79.8, 60.4, 42.7, 35.4, 31.7, 29.3, 28.5, 27.9, 27.0, 26.9, 26.7, 26.4, 22.6, 19.4, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{56}NO_5Si$ 610.39223, found 610.39431.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-phenyloct-2-enyl 2-(*tert*-Butoxycarbonylamino)acetate (11e). Prepared from **10e** using the same three-step procedure described for the **10a** → **11a** reaction (55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.52 (m, 4H), 7.45−7.28 (m, 11H), 6.63 (m, 1H), 5.59 (t, J = 7.4 Hz, 1H), 4.97 (m, 1H), 4.20 (m, 1H), 3.96 (m, 3H), 1.88 (m, 2H), 1.45 (s, 9H), 1.32−1.06 (m, 6H), 1.01 (s, 9H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 155.7, 138.5, 135.8, 135.7, 133.43, 133.36, 131.0, 129.8, 129.7, 128.4, 128.1, 127.78, 127.75, 127.7, 80.0, 59.4, 42.8, 31.6, 29.4, 28.5, 27.7, 27.0, 26.9, 22.6, 19.3, 14.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{38}H_{51}NO_5SiNa$ 652.34287, found 652.34622.

(*E*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-phenylbut-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate (11f). Prepared from **10f** using the same three-step procedure described for the **10a** → **11a** reaction (35%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 4H), 7.44−7.31 (m, 7H), 7.18 (m, 4H), 6.67 (s, 1H), 5.76 (q, J = 6.6 Hz, 1H), 4.97 (m, 1H), 4.35 (s, 2H), 3.95−3.51 (m, 2H), 1.51 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 155.8, 139.9, 136.2, 135.8, 135.8, 133.32, 133.27, 129.8, 129.1, 129.0, 128.2, 127.8, 127.3, 80.0, 73.2, 60.2, 42.8, 28.5, 27.0, 20.4, 19.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{34}H_{43}NO_5SiNa$ 596.28027, found 596.28242.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-phenylpent-1-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11g). Prepared from **10g** using the same three-step procedure described for the **10a** → **11a** reaction (30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dt, J = 8.0, 1.6 Hz, 4H), 7.44−7.31 (m, 7H), 7.20 (s, 4H), 6.64 (s, 1H), 5.54 (t, J = 6.6 Hz, 1H), 4.96 (m, 1H), 4.33 (q, J = 11.7 Hz, 2H), 4.03−3.76 (m, 2H), 1.98−1.75 (m, 2H), 1.45 (s, 9H), 1.07 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 155.7, 138.2, 136.2, 135.77, 135.75, 133.3, 133.2, 130.4, 129.79, 129.77, 129.0, 128.1, 127.8, 127.2, 79.9, 78.8, 60.1, 42.7, 28.4, 27.2, 27.0, 19.3, 10.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{35}H_{45}NO_5SiNa$ 610.29592, found 610.29312.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-methyl-1-phenylpent-1-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11h). Prepared from **10h** using the same three-step procedure described for the **10a** → **11a** reaction (35%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.46−7.31 (m, 7H), 7.22 (m, 4H), 6.61 (s, 1H), 5.35 (d, J = 7.1, 1H), 4.95 (bs, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 4.00−3.81 (m, 2H), 2.17 (m, 1H), 1.45 (s, 9H), 1.08 (s, 9H), 0.95 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 155.7, 137.2, 136.2, 135.9, 133.3, 133.2, 131.6, 129.9, 129.8, 129.1, 128.2, 127.78, 127.77, 127.3, 82.9, 80.0, 60.0, 42.6, 30.9, 28.4, 27.0, 19.8, 19.4, 17.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{36}H_{47}NO_5SiNa$ 624.31157, found 624.31511.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-4,4-dimethyl-1-phenylpent-1-en-3-yl 2-(*tert*-Butoxycarbonylamino)acetate (11i). Prepared from **10i** using the same three-step procedure described for the **10a** → **11a** reaction (51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.44−7.29 (m, 6H), 7.25−7.16 (m, 5H), 6.64 (s, 1H), 5.47 (s, 1H), 4.93 (bs, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.23 (d, J = 12.2 Hz, 1H), 3.97−3.71 (m, 2H), 1.45 (s, 9H), 1.05 (s, 9H), 0.93 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 155.7, 138.0, 136.4, 136.0, 135.8, 133.4, 133.3, 132.1, 129.8, 129.7, 129.1, 128.2, 127.8, 127.7, 127.2, 81.9, 79.9, 61.6, 42.8, 35.9, 28.5, 27.0, 26.5, 19.4; HRMS

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(ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{37}H_{49}NO_5SiNa$ 638.32722, found 638.32163.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,3-diphenylallyl 2-(*tert*-Butoxycarbonylamino)acetate (11j). Prepared from **10j** using the same three-step procedure described for the **10a** → **11a** reaction (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 20.2, 7.8 Hz, 4H), 7.41−7.27 (m, 12H), 7.23−7.15 (m, 5H), 6.78 (s, 1H), 6.73 (s, 1H), 4.98 (m, 1H), 4.36 (d, J = 11.9 Hz, 1H), 4.07 (d, J = 12.0 Hz, 1H), 3.97 (d, J = 5.3 Hz, 2H), 1.44 (d, J = 6.5 Hz, 9H), 1.03 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 155.7, 138.4, 138.1, 136.1, 136.0, 135.8, 135.7, 133.3, 133.1, 129.8, 129.7, 129.5, 129.0, 128.9, 128.6, 128.4, 128.2, 128.0, 127.76, 127.75, 127.6, 127.3, 126.7, 80.1, 60.0, 42.8, 28.5, 27.1, 26.9, 19.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{39}H_{45}NO_5SiNa$ 658.29592, found 658.29583.

(*E*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-phenylbut-2-enyl 2-(*tert*-Butoxycarbonylamino)acetate (11k). Prepared from **10k** using the same three-step procedure described for the **10a** → **11a** reaction (72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.9, 1.4 Hz, 2H), 7.56 (dd, J = 7.9, 1.3 Hz, 2H), 7.47−7.27 (m, 11H), 6.64 (s, 1H), 5.65 (m, 1H), 4.98 (m, 1H), 4.21 (d, J = 12.1 Hz, 1H), 4.03 (d, J = 12.1 Hz, 1H), 3.94 (d, J = 5.3 Hz, 2H), 1.52 (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 155.7, 138.5, 136.9, 135.7, 135.6, 133.42, 133.35, 129.73, 129.67, 128.4, 128.1, 127.74, 127.71, 127.6, 125.2, 79.9, 77.3, 59.2, 42.7, 28.4, 26.8, 19.2, 13.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{34}H_{43}NO_5SiNa$ 596.28027, found 596.28307.

(*E*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]hex-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate (11l). Prepared from **10l** using the same three-step procedure described for the **10a** → **11a** reaction (53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.61 (m, 4H), 7.47−7.35 (m, 6H), 5.61 (q, J = 6.4 Hz, 1H), 5.54 (t, J = 7.3 Hz, 1H), 4.92 (bs, 1H), 4.21 (m, 2H), 3.92−2.73 (m, 2H), 1.87 (m, 2H), 1.43 (m, 12H), 1.04 (s, 9H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 155.7, 136.71, 135.67, 135.7, 134.9, 133.54, 133.47, 131.8, 129.8, 127.8, 79.8, 73.4, 59.5, 42.8, 28.4, 26.9, 20.8, 20.0, 19.3, 14.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{30}H_{44}NO_5Si$ 526.29833, found 526.29901.

(*Z*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]but-2-enyl 2-(*tert*-Butoxycarbonylamino)acetate (11m). Prepared from **10m**[24] using the same three-step procedure described for the **10a** → **11a** reaction (95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.46−7.36 (m, 6H), 5.65 (q, J = 7.0 Hz, 1H), 4.98 (bs, 1H), 4.76 (s, 2H), 4.25 (s, 2H), 3.92−3.76 (m, 2H), 1.50−1.43 (m, 12H), 1.04 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 155.7, 135.7, 133.6, 133.5, 129.9, 127.8, 127.4, 80.1, 67.4, 59.2, 42.6, 28.5, 26.9, 19.4, 13.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{40}NO_5Si$ 498.26703, found 498.26692.

(*E*)-2-[(Triisopropylsilyloxy)methyl]but-2-enyl 2-(*tert*-Butoxycarbonylamino)acetate (11n). Prepared from **10n**[24] using the same three-step procedure described for the **10a** → **11a** reaction (99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (q, J = 7.0 Hz, 1H), 5.00 (s, 1H), 4.74 (s, 2H), 4.19 (s, 2H), 3.89 (d, J = 5.0 Hz, 2H), 1.73 (d, J = 7.0 Hz, 3H), 1.44 (s, 9H), 1.16−1.01 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 155.8, 133.7, 126.3, 80.1, 65.5, 60.5, 42.5, 28.4, 18.1, 13.2, 12.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{42}NO_5Si$ 416.28268, found 416.28138.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-3-[(*Z*)-1-(*tert*-butyldiphenylsilyloxy)but-2-en-2-yl]octanoic Acid (13a).** A solution of NaHMDS (1 M in THF, 3.43 mL, 3.43 mmol) was diluted with 3 mL of additional THF at rt and treated with a solution of **11a** (690 mg, 1.35 mmol) in 5 mL of THF. After TLC indicated consumption of the starting material (typically within 20 min), the reaction was quenched with 1 M aq HCl and the mixture evaporated under reduced pressure. The residue was taken up in 1 M aq HCl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (10% EtOAc/hexane) to give alcohol (0.082 mg, 18%) and then 10% MeOH/EtOAc to afford carboxylic acid **13a** as a sticky foam (501 mg, 77%). It should be noted that column chromatography was performed only to remove the byproduct and that the column flushing stage presumably provides an inseparable mixture of diastereomeric carboxylic acids. This semicrude mixture was used in the next step without further purification. Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.49−7.38 (m, 6H), 5.48 (m, 1H), 5.33 (d, J = 8.6 Hz, 1H), 4.53 (m, 1H), 4.25 (m, 1H), 4.06 (m, 1H), 2.63 (m, 1H), 1.59−1.35 (m, 15H), 1.32−1.12 (m, 3H), 1.05 (m, 11H), 0.83 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 155.7, 135.9, 135.8, 135.3, 132.4, 130.2, 130.1, 128.1, 128.0, 79.8, 60.2, 57.5, 48.2, 31.8, 31.1, 28.7, 28.5, 28.4, 27.2, 27.0, 22.6, 19.2, 14.2, 13.5; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{33}H_{48}NO_5Si$ 566.33072, found 566.33285.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-3-[(*Z*)-1-(*tert*-butyldiphenylsilyloxy)pent-2-en-2-yl]octanoic Acid (13b).** Prepared from **11b** using the same procedure described for the **11a** → **13a** reaction (60%). Spectral data given for the mixture of rotamers and diastereomers (91:9 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.65 (m, 4H), 7.50−7.36 (m, 6H), 5.44 (t, J = 7.4 Hz, 1H), 5.27 (m, 1H), 4.58 (m, 1H), 4.32−4.15 (m, 1H), 4.08−3.92 (m, 1H), 2.40 (m, 1H), 1.97−1.78 (m, 2H), 1.56 (m, 1H), 1.43 (m, 11H), 1.33−1.11 (m, 2H), 1.06 (m, 12H), 0.91−0.77 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 155.7, 135.9, 135.8, 134.9, 134.3, 134.1, 132.8, 132.7, 130.0, 130.0, 128.0, 127.9, 127.8, 79.7, 60.7, 57.4, 46.8, 31.8, 28.8, 28.5, 27.1, 27.0, 22.6, 21.1, 19.2, 14.3, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{34}H_{52}NO_5Si$ 582.3609, found 582.3664.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-3-[(*Z*)-1-(*tert*-butyldiphenylsilyloxy)-4-methylpent-2-en-2-yl]octanoic Acid (13c).** Prepared from **11c** using the same procedure described for the **11a** → **13a** reaction (62%). Spectral data given for the mixture of rotamers and diastereomers (90:10 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 4H), 7.42 (m, 6H), 5.74−5.46 (m, 0.5H), 5.39 (d, J = 8.3 Hz, 0.5H), 5.29−5.03 (m, 1H), 4.67−4.39 (m, 1H), 4.31−3.90 (m, 2H), 2.82−2.48 (m, 1H), 2.28 (m, 1H), 1.71−1.37 (m, 10H), 1.36−1.02 (m, 16H), 1.01−0.66 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7, 176.9, 158.2, 156.5, 155.7, 139.1, 136.0, 135.81, 135.76, 135.7, 134.9, 133.3, 133.0, 132.9, 132.3, 129.9, 127.9, 127.81, 127.77, 127.7, 80.5, 79.8, 79.7, 61.1, 57.2, 45.6, 40.6, 31.8, 31.6, 31.5, 28.8, 28.49, 28.45, 28.3, 26.97, 26.92, 26.9, 26.9, 26.7, 23.11, 23.06, 22.9, 22.6, 22.5, 19.2, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$calcd for $C_{35}H_{54}NO_5Si$ 596.3766, found 596.3808.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-3-[(*Z*)-1-(*tert*-butyldiphenylsilyloxy)-4,4-dimethylpent-2-en-2-yl]octanoic Acid (13d).** Prepared from **11d** using the same procedure described for the **11a** → **13a** reaction (52%). Spectral data given for the mixture of rotamers and diastereomers (83:17 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.66 (m, 4H), 7.43 (m, 6H), 5.44 (m, 1H), 5.24 (m, 1H), 4.61 (m, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.02 (m, 1H), 2.24 (m, 1H), 1.55 (m, 1H), 1.43 (m, 10H), 1.26 (m, 1H), 1.18 (m, 1H), 1.07 (m, 13H), 0.88 (m, 9H), 0.81 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 155.6, 136.0, 134.9, 133.6, 132.8, 130.0, 127.9, 127.8, 79.6, 61.0, 57.3, 32.5, 31.8, 31.3, 28.8, 28.5, 27.1, 27.0, 22.7, 19.2, 14.1; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{36}H_{54}NO_5Si$ 608.37767, found 608.37878.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-3-[(*Z*)-3-(*tert*-butyldiphenylsilyloxy)-1-phenylprop-1-en-2-yl]octanoic Acid (13e).** Prepared from **11e** using the same procedure described for the **11a** → **13a** reaction (74%). Spectral data given for the mixture of rotamers and diastereomers (87:13 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.27 (m, 10H), 7.21 (m, 3H), 7.09 (m, 2H), 6.56 (s, 1H), 5.30 (m, 1H), 4.71 (m, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 2.69 (m, 1H), 1.62 (m, 1H), 1.45 (m, 10H), 1.30−1.12 (m, 4H), 1.08 (m, 11H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 155.7, 138.2, 136.9, 135.9, 135.8, 134.9, 132.8, 130.7, 130.0, 129.9, 129.8, 128.9, 128.1, 127.9, 127.8, 126.9, 79.9, 61.7, 56.8, 53.5, 45.8, 31.9, 28.44, 28.35, 27.1, 27.0, 22.7, 19.3, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{38}H_{51}NO_5SiNa$ 652.3429, found 652.3426.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-phenylhex-4-enoic Acid (13f).** Prepared from **11f** using the same procedure described for the **11a** → **13a** reaction (85%). Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.70 (m, 2H), 7.60 (m, 2H), 7.50−7.30 (m, 8H), 7.25−7.10 (m, 4H), 5.79 (q, J = 6.9 Hz, 1H), 5.08 (m, 1H), 4.81 (d, J = 8.2 Hz, 1H), 4.08−3.87 (m, 3H), 1.52 (d, J = 6.9 Hz, 3H), 1.41 (m, 9H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 155.6, 138.1, 137.2, 135.8, 135.6, 134.9, 133.0, 132.9, 129.8, 129.8, 129.1, 128.6, 127.82, 127.77, 127.3, 125.0, 80.2, 80.1, 60.1, 55.9, 51.0, 31.0, 28.4, 28.3, 26.9, 26.7, 19.2, 13.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{44}NO_5Si$ 574.2983, found 574.3026.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-phenylhept-4-enoic Acid (13g).** Prepared from **11g** using the same procedure described for the **11a** → **13a** reaction (76%). Spectral data given for the mixture of rotamers and diastereomers (87:13 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2.5H), 7.57 (m, 1.5H), 7.47−7.31 (m, 7H), 7.30−7.16 (m, 4H), 5.66 (t, J = 7.3 Hz, 1H), 5.04 (m, 1H), 4.83 (m, 1H), 4.18−3.87 (m, 3H), 1.89 (m, 2H), 1.39 (m, 9H), 1.08 (m, 9H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 174.4, 156.0, 155.5, 138.1, 135.8, 135.7, 134.9, 134.1, 133.0, 132.9, 132.8, 129.9, 129.8, 129.1, 128.6, 128.4, 127.9, 127.82, 127.77, 127.3, 80.6, 80.3, 80.1, 60.3, 56.0, 51.1, 42.4, 28.4, 28.3, 27.0, 26.9, 21.3, 21.2, 19.2, 19.1, 14.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{46}NO_5Si$ 588.3140, found 588.3180.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-6-methyl-3-phenylhept-4-enoic Acid (13h).** Prepared from **11h** using the same procedure described for the **11a** → **13a** reaction (54%). Spectral data given for the mixture of rotamers and diastereomers (79:21 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.57 (m, 4H), 7.39 (m, 7H), 7.26−7.14 (m, 4H), 5.51 (d, J = 9.7 Hz, 1H), 5.46−5.16 (m, 1H), 5.15−4.96 (m, 1H), 4.78 (m, 0.5H), 4.55 (m, 0.5H), 3.99 (m, 2H), 2.62 (m, 0.5H), 2.29 (m, 0.5H), 1.39 (m, 9H), 1.05 (m, 9H), 1.00−0.80 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 176.5, 156.5, 155.3, 143.8, 139.4, 138.5, 138.1, 136.0, 135.81, 135.76, 135.7, 133.8, 133.2, 133.1, 132.9, 132.0, 129.9, 129.8, 129.1, 128.6, 128.4, 128.0, 127.9, 127.82, 127.76, 127.2, 126.6, 80.1, 80.0, 67.4, 60.5, 55.9, 55.2, 51.0, 45.4, 28.5, 28.3, 27.21, 27.16, 27.0, 26.9, 23.2, 23.0, 22.7, 19.2, 19.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{48}NO_5Si$ 602.3296, found 602.3332.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-6,6-dimethyl-3-phenylhept-4-enoic Acid (13i).** Prepared from **11i** using the same procedure described for the **11a** → **13a** reaction (61%). Spectral data given for the mixture of rotamers and diastereomers (78:22 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.48−7.30 (m, 7H), 7.24−7.08 (m, 4H), 5.74 (s, 1H), 5.12 (t, J = 9.6 Hz, 1H), 4.78 (d, J = 9.4 Hz, 1H), 4.14 (d, J = 11.5 Hz, 1H), 3.99 (d, J = 12.0 Hz, 1H), 3.90 (d, J = 9.6 Hz, 1H), 1.37 (s, 9H), 1.12 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 155.3, 140.6, 138.2, 136.0, 135.9, 135.5, 133.0, 132.9, 129.9, 129.8, 129.1, 128.6, 127.8, 127.7, 127.2, 80.0, 60.4, 56.1, 50.9, 32.7, 31.4, 28.4, 27.0, 19.2; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{37}H_{48}NO_5Si$ 614.33072, found 614.33277.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3,5-diphenylpent-4-enoic Acid (13j).** Prepared from **11j** using the same procedure described for the **11a** → **13a** reaction (69%). Spectral data given for the mixture of rotamers and diastereomers (73:27 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.58 (m, 1H), 7.50−7.07 (m, 18H), 6.82 (s, 1H), 5.16 (m, 0.5H), 4.94 (m, 0.5H), 4.87−4.63 (m, 1H), 4.35 (m, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 1.39 (m, 9H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 156.1, 155.6, 139.6, 138.5, 137.5, 136.9, 136.7, 135.9, 135.8, 135.7, 133.5, 133.13, 133.09, 132.9, 130.0, 129.9, 129.74, 129.65, 129.3, 128.9, 128.8, 128.6, 128.6, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 127.0, 80.2, 65.7, 61.2, 55.8, 55.1, 50.1, 45.5, 28.5, 28.3, 28.1, 27.0, 26.9, 19.3, 19.2, 19.2; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{39}H_{46}NO_5SiNa$ 658.2959, found 658.2968.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methyl-5-phenylpent-4-enoic Acid (13k).** Prepared from **11k** using the same procedure described for the **11a** → **13a** reaction (78%). Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.53 (m, 4H), 7.43−7.23 (m, 7H), 7.20−6.96 (m, 4H), 6.40 (s, 1H), 5.28 (d, J = 8.8 Hz, 1H), 4.77 (d, J = 8.5, 4.2 Hz, 1H), 4.48 (q, J = 12.5 Hz, 2H), 3.36 (m, 1H), 1.34 (m, 9H), 1.17 (d, J = 6.9 Hz, 3H), 1.06 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 155.7, 140.7, 136.8, 135.8, 135.7, 133.1, 133.0, 129.8, 129.7, 129.1, 128.9, 128.6, 128.0, 127.9, 127.8, 126.8, 79.9, 61.4, 56.3, 39.4, 28.43, 28.38, 27.0, 19.4, 14.2; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{34}H_{42}NO_5Si$ 572.28377, found 572.28566.

(2*S,3*R**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-ethylhex-4-enoic Acid (13l).** Prepared from **11l** using the same procedure described for the **11a** → **13a** reaction (89%). Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (bs, 1H), 7.74 (m, 4H), 7.43 (m, 6H), 5.52 (m, 1H), 4.57 (m, 1H), 4.33 (m, 1H), 4.13 (m, 1H), 2.74 (m, 1H), 1.61 (m, 1H), 1.42 (m, 13H), 1.09 (s, 9H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 155.7, 135.9, 135.8, 135.0, 132.6, 132.5, 130.1, 128.03, 127.97, 125.3, 104.9, 79.8, 60.2, 57.3, 49.8, 28.5, 27.0, 21.8, 19.3, 13.5, 12.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{44}NO_5Si$ 526.29833, found 526.29965.

(2*S,3*R**)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylpent-4-enoic Acid (13m).** Prepared from **11m** using the same procedure described for the **11a** → **13a** reaction (82%). Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (bs, 1H), 7.67 (m, 4H), 7.41 (m, 6H), 5.22 (s, 1H), 5.10 (m, 1H), 4.95 (m, 1H), 4.70−4.40 (m, 1H), 4.40−4.04 (m, 2H), 2.90 (m, 1H), 1.49−1.31 (m, 9H), 1.15−0.99 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 155.6, 148.1, 135.7, 133.4, 129.8, 127.85, 127.82, 111.9, 80.1, 66.1, 56.3, 38.0, 28.4, 26.9, 19.4, 14.5; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{28}H_{38}NO_5Si$ 496.25247, found 496.25222.

(2*S,3*S**)-2-(*tert*-Butoxycarbonylamino)-3-methyl-4-[(triisopropylsilyloxy)methyl]pent-4-enoic Acid (13n).** Prepared from **11n** using the same procedure described for the **11a** → **13a** reaction (65%). Spectral data given for the mixture of rotamers and diastereomers (94:6 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.63 (m, 1H), 5.22 (s, 1H), 5.04 (s, 1H), 4.32−4.12 (m, 3H), 2.84 (m, 1H), 1.44 (m, 9H), 1.15 (m, 3H), 1.07 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 156.1, 147.8, 134.8, 114.8, 80.1, 65.9, 58.0, 39.1, 28.4, 18.1, 16.7, 12.1, 12.0; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{21}H_{40}NO_5Si$ 414.26812, found 414.26687.

(*S*)-*tert*-Butyl 2-{(2*R*,3*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylhex-4-enamido}-4-methylpentanoate (14) and (*S*)-*tert*-Butyl 2-{(2*S*,3*R*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)-methyl]-3-methylhex-4-enamido)-4-methylpentanoate (15). A solution of **13a** (810 mg, 1.43 mmol) in 12 mL of MeCN was treated with HBTU (0.704 g, 1.86 mmol), HOBt (0.039 g, 0.285 mmol), NEt_3 (1.19 mL, 8.57 mmol), and H-Leu-O*t*Bu-HCl (0.415 g, 1.86 mmol). After being stirred at rt for 20 h, the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 1 M aq HCl followed by 10% aq Na_2CO_3. The organic layer was dried over Na_2SO_4 and evaporated. Purification by flash column chromatography over silica gel (5−7.5% EtOAc/hexanes and then 30%) afforded the diastereomeric dipeptides in 76% combined yield.

Data for **14** (37%): $[\alpha]^{24}_D$ −6.3 (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.59 (m, 4H), 7.41 (m, 6H), 6.33 (d, J = 8.4 Hz, 1H), 5.35 (q, J = 6.7 Hz, 2H), 4.47 (td, J = 8.7, 5.7 Hz, 1H), 4.38−4.07 (m, 3H), 2.77 (m, 1H), 1.63 (m, 1H), 1.52 (m, 2H), 1.57−1.34 (m, 26H), 1.32−1.13 (m, 4H), 1.13−1.01 (m, 10H), 0.89 (m, 6H), 0.83 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.3, 155.6, 136.7, 135.9, 135.8, 133.4, 133.2, 129.9, 129.8, 127.9, 127.8, 124.6, 81.7, 61.1, 51.2, 46.2, 42.1, 32.1, 28.4, 28.1, 27.4, 27.2, 24.8, 22.9, 22.7, 22.1, 19.3, 14.2, 13.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{43}H_{69}N_2O_6Si$ 737.49249, found 737.49350.

Data for **15** (38%): $[\alpha]^{24}_D$ −0.5 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.64 (m, 4H), 7.41 (m, 6H), 6.49 (d, J = 7.6 Hz, 1H), 5.37 (q, J = 6.8 Hz, 1H), 5.25 (bs, 1H), 4.44 (dd, J = 14.2, 8.3 Hz, 1H), 4.39−4.19 (m, 1H), 4.08 (d, J = 12.0 Hz, 1H), 2.63 (m, 1H), 1.62 (m, 1H), 1.55−1.35 (m, 25H), 1.30−1.15 (m, 3H), 1.15−1.01 (m, 12H), 0.89 (m, 6H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.5, 155.7, 136.1, 136.0, 134.9, 133.5, 133.2, 129.9, 129.7, 127.9, 127.8, 125.5, 81.5, 60.8, 58.0, 51.3, 47.6, 42.4, 32.0,

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28.6, 28.5, 28.1, 27.3, 27.2, 26.7, 24.9, 22.8, 22.7, 22.4, 19.3, 14.2, 13.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{43}H_{69}N_2O_6Si$ 737.49249, found 737.49130.

(*R*)-*tert*-Butyl 2-[(2*R*,3*S*,*Z*)-4-Ethylidene-3-pentylpyrrolidine-2-carboxamido]-4-methylpentanoate (16). A solution of **14** (375 mg, 0.509 mmol) in 4 mL of THF and 1.5 mL of pyridine in a polypropylene flask was cooled to 0 °C and treated with HF (70% solution in pyridine, 1.50 mL). After the mixture had been stirred for 5 h at rt, TLC indicated completion and the reaction was quenched by careful addition of saturated aq $NaHCO_3$. The mixture was extracted with EtOAc, and the organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (10−20% EtOAc/hexanes) afforded the intermediate alcohol as a white foam (220 mg, 87%): $[\alpha]^{24}_D$ −8.5 (*c* 2.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 6.7 Hz, 1H), 5.42 (q, *J* = 6.8 Hz, 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.41 (m, 1H), 4.32 (m, 1H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.12 (d, *J* = 11.5 Hz, 1H), 3.12 (bs, 1H), 2.49−2.26 (m, 1H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.64−1.36 (m, 24H), 1.31−1.00 (m, 6H), 0.91 (m, 6H), 0.83 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.7, 156.0, 137.1, 127.3, 82.0, 80.1, 67.8, 59.3, 57.9, 51.4, 49.4, 42.0, 31.9, 29.3, 28.4, 28.1, 27.2, 24.9, 24.1, 22.9, 22.7, 22.1, 14.2, 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{51}N_2O_6$ 499.37471, found 499.37534.

A solution of alcohol described above (215 mg, 0.431 mmol) in 2 mL of CH_2Cl_2 was cooled to 0 °C and treated with NEt_3 (0.430 mL, 3.09 mmol) and methanesulfonyl chloride (0.203 mL, 2.65 mmol). The reaction mixture was stirred at rt for 18 h, diluted with CH_2Cl_2, and washed with 1 M aq HCl. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography to give the intermediate allylic chloride as a white solid (210 mg, 94%): $[\alpha]^{24}_D$ −20.5 (*c* 2.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 8.2 Hz, 1H), 5.58 (q, *J* = 6.9 Hz, 1H), 5.08 (d, *J* = 41.4 Hz, 1H), 4.45 (dd, *J* = 13.9, 8.4 Hz, 1H), 4.29−4.12 (m, 2H), 4.05 (d, *J* = 11.5 Hz, 1H), 2.66−2.54 (m, 1H), 1.73 (d, *J* = 6.9 Hz, 3H), 1.69−1.50 (m, 3H), 1.49−1.39 (m, 21H), 1.31−1.05 (m, 6H), 0.92 (m, 6H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.8, 155.7, 134.6, 129.9, 82.1, 80.0, 57.4, 51.5, 48.4, 42.1, 41.2, 31.9, 28.4, 28.1, 27.8, 27.0, 25.0, 22.9, 22.6, 22.2, 14.2, 13.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{50}ClN_2O_5$ 517.34083, found 517.33905.

The allylic chloride mentioned above (160 mg, 0.309 mmol) was treated with a solution of 15% TFA in CH_2Cl_2 (2.5 mL) precooled to 0 °C. The mixture was stirred at 0 °C for 3 h, diluted with EtOAc, and concentrated under reduced pressure. The dilution−concentration sequence was repeated two more times, and the crude TFA salt was dried under vacuum. The residue was then taken up in 3.0 mL of acetone, and K_2CO_3 (426 mg, 3.09 mmol) was added. After being stirred at rt for 20 h, the mixture was filtered through Celite, concentrated, and purified by flash chromatography (90−100% EtOAc/hexanes eluent) to afford **16** as a thick colorless oil (67.0 mg, 58%, two steps): $[\alpha]^{24}_D$ −54.0 (*c* 1.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 6.8 Hz, 1H), 6.09 (bs, 2H), 5.46 (m, 1H), 4.64 (m, 1H), 4.41 (m, 1H), 4.10 (m, 1H), 3.92 (m, 1H), 2.91 (m, 1H), 1.79−1.51 (m, 6H), 1.42 (m, 11H), 1.35−1.16 (m, 6H), 0.89 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 166.9, 134.8, 119.6, 83.1, 63.0, 51.8, 46.4, 45.1, 40.6, 31.9, 27.9, 27.2, 25.0, 22.9, 22.5, 21.5, 14.7, 14.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{41}N_2O_3$ 381.31172, found 381.31360.

(*R*)-*tert*-Butyl 2-[(2*R*,3*S*,*Z*)-4-Ethylidene-3-pentylpyrrolidine-2-carboxamido]-4-methylpentanoate (17). Prepared from **15** following the same three-step procedure used for the **14** → **16** reaction.

Data for the primary alcohol intermediate (85%): $[\alpha]^{24}_D$ −15.2 (*c* 2.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.5 Hz, 1H), 5.43 (q, *J* = 6.8 Hz, 1H), 5.11 (d, *J* = 9.0 Hz, 1H), 4.48 (td, *J* = 9.1, 5.2 Hz, 1H), 4.26 (m, 2H), 4.02 (m, 1H), 2.66 (bs, 1H), 2.33 (t, *J* = 8.8 Hz, 1H), 1.64 (m, 4H), 1.60−1.48 (m, 2H), 1.44 (m, 20H), 1.33−0.98 (m, 6H), 0.91 (m, 6H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 171.9, 156.0, 136.9, 128.6, 82.3, 79.9, 67.8, 58.3, 58.2, 51.1, 50.4, 42.1, 31.9, 28.8, 28.4, 28.1, 27.2, 24.9, 23.0, 22.7, 22.0, 14.2, 13.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{51}N_2O_6$ 499.37471, found 499.37470.

Data for the allylic chloride intermediate (86%): $[\alpha]^{24}_D$ +6.9 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (m, 1H), 5.61 (q, *J* = 6.9 Hz, 1H), 5.07 (d, *J* = 8.4 Hz, 1H), 4.44 (td, *J* = 8.5, 5.6 Hz, 1H), 4.17 (m, 2H), 4.04 (d, *J* = 11.5 Hz, 1H), 2.52 (m, 1H), 1.73 (d, *J* = 6.9 Hz, 3H), 1.68−1.50 (m, 3H), 1.46 (m, 20H), 1.36−1.08 (m, 6H), 0.92 (m, 6H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.9, 155.8, 134.5, 130.2, 82.0, 80.0, 58.0, 51.5, 48.4, 42.3, 41.5, 32.0, 28.4, 28.1, 27.0, 25.0, 22.9, 22.6, 22.3, 14.2, 13.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{50}ClN_2O_5$ 517.34083, found 517.34350.

Data for **17** (56%): $[\alpha]^{24}_D$ −32.5 (*c* 2.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 1H), 5.49 (d, *J* = 6.9 Hz, 1H), 4.61 (m, 1H), 4.43 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.02 (m, 2H), 2.91 (m, 1H), 1.71−1.49 (m, 6H), 1.44 (s, 9H), 1.40−1.16 (m, 8H), 1.00−0.79 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 166.0, 134.5, 121.1, 82.3, 63.7, 52.0, 45.5, 45.2, 40.9, 31.5, 28.0, 27.9, 26.5, 24.9, 22.7, 22.6, 21.7, 14.7, 14.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{41}N_2O_3$ 381.31172, found 381.31310.

(*S*)-*tert*-Butyl 2-{(2*R*,3*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methyl-5-phenylpent-4-enamido}-4-methylpentanoate (18) and (*S*)-*tert*-Butyl 2-{(2*S*,3*R*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methyl-5-phenylpent-4-enamido}-4-methylpentanoate (19). Prepared from racemic **13e** following the same procedure described for the **13a** → **14**/**15** reaction. Careful flash chromatography over silica gel afforded the diastereomeric dipeptides in 77% combined yield.

Data for **18** (37%): $[\alpha]^{24}_D$ +8.1 (*c* 2.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.48−7.27 (m, 6H), 7.21−6.98 (m, 5H), 6.40 (s, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 5.37 (m, 1H), 4.58−4.19 (m, 4H), 3.02 (m, 1H), 1.71−1.45 (m, 4H), 1.41 (m, 20H), 1.31−1.13 (m, 5H), 1.09 (s, 9H), 0.98−0.75 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.1, 155.6, 138.9, 136.9, 135.9, 135.8, 133.21, 133.17, 129.8, 129.7, 129.0, 128.0, 127.9, 127.8, 126.7, 81.8, 62.1, 57.5, 51.3, 46.2, 42.0, 32.1, 28.4, 28.3, 28.1, 28.0, 27.3, 27.2, 24.8, 22.7, 22.1, 19.4, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{48}H_{71}N_2O_6Si$ 799.50759, found 799.50832.

Data for **19** (40%): $[\alpha]^{24}_D$ −10.7 (*c* 2.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.62 (m, 2H), 7.48−7.28 (m, 6H), 7.24−7.03 (m, 5H), 6.40 (m, 2H), 5.32 (d, *J* = 7.5 Hz, 1H), 4.43 (m, 3H), 4.28 (m, 1H), 3.00 (m, 1H), 1.58 (m, 4H), 1.49−1.32 (m, 21H), 1.30−1.17 (m, 4H), 1.09 (m, 9H), 0.84 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.2, 155.7, 139.0, 137.0, 136.0, 135.9, 133.3, 129.9, 129.8, 129.7, 129.0, 128.8, 128.6, 127.9, 127.8, 127.7, 126.7, 81.7, 62.2, 57.6, 51.5, 46.2, 42.2, 32.1, 28.5, 28.4, 28.1, 28.0, 27.2, 27.1, 24.9, 22.8, 22.7, 22.4, 19.4, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{48}H_{70}N_2O_6Si$ 799.50759, found 799.50980; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{48}H_{70}N_2O_6SiNa$ 821.48954, found 821.49194.

(*S*)-*tert*-Butyl 2-[(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3-chloro-3-phenylprop-1-en-2-yl)octanamido]-4-methylpentanoate (20). Prepared from **18** following the same desilylation/chlorination sequence described for the **14** → **16** reaction.

Data for the primary alcohol intermediate (88%): $[\alpha]^{24}_D$ −19.4 (*c* 1.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 7.21 (m, 1H), 6.45 (s, 1H), 5.44 (d, *J* = 8.7 Hz, 1H), 4.52 (t, *J* = 8.8 Hz, 1H), 4.41 (m, 2H), 4.24 (d, *J* = 10.8 Hz, 1H), 4.08 (m, 1H), 2.55 (m, 1H), 1.73−1.47 (m, 2H), 1.40 (m, 21H), 1.31−1.10 (m, 6H), 0.92−0.67 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.7, 156.1, 138.8, 136.6, 132.8, 129.1, 128.2, 127.1, 81.8, 80.1, 59.9, 57.9, 51.6, 50.3, 42.0, 31.9, 29.5, 28.4, 28.0, 27.1, 24.8, 22.6, 22.6, 22.0, 14.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{53}N_2O_6$ 561.39037, found 561.38990.

Data for the diastereomeric mixture of allylic chlorides **20** (87%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.16 (m, 6H), 6.14 (d, *J* = 8.3 Hz, 0.5H), 5.91 (d, *J* = 8.2 Hz, 0.5H), 5.48 (s, 0.5H), 5.35 (s, 0.5H), 5.24 (d, *J* = 1.8 Hz, 0.5H), 5.12 (d, *J* = 1.5 Hz, 0.5H), 4.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.68 (d, *J* = 8.6 Hz, 0.5H), 4.52 (m, 1.5H), 2.99 (m, 1H), 1.74−1.51 (m, 3H), 1.47 (m, 11H), 1.38 (m, 5H), 1.33−1.16 (m, 4H),

1.11 (s, 5H), 0.93 (m, 6H), 0.86 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 172.0, 170.0, 169.8, 154.0, 153.6, 151.9, 150.5, 144.1, 142.6, 128.9, 128.7, 128.6, 128.5, 127.3, 127.1, 125.1, 124.8, 107.4, 106.9, 82.1, 81.8, 81.0, 80.3, 66.9, 66.6, 65.1, 64.0, 51.6, 51.3, 51.3, 47.9, 43.9, 43.7, 43.4, 42.8, 42.2, 42.0, 32.3, 32.2, 28.4, 28.2, 28.1, 28.0, 26.9, 26.5, 26.2, 24.9, 24.8, 22.9, 22.7, 22.6, 22.5, 22.2, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{52}ClN_2O_5$ 579.35593, found 579.35436; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{32}H_{51}ClN_2O_5Na$ 601.33787, found 601.33641.

(*R*)-*tert*-Butyl 4-Methyl-2-[(2*R*,3*S*,5*S*)-4-methylene-3-pentyl-5-phenylpyrrolidine-2-carboxamido]pentanoate (21). Prepared from **20** following the same deprotection/cyclization procedure described for the **14** → **16** reaction (60%): $[\alpha]^{26}_D$ +7.3 (*c* 2.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 1H), 7.34 (m, 2H), 7.26 (m, 3H), 4.98 (m, 1H), 4.86 (s, 1H), 4.55 (m, 2H), 4.19 (d, *J* = 6.7 Hz, 1H), 2.95 (dd, *J* = 13.4, 6.8 Hz, 1H), 1.93 (bs, 1H), 1.61 (m, 2H), 1.51 (m, 1H), 1.43 (m, 12H), 1.28 (m, 5H), 0.93 (m, 6H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.1, 155.0, 144.6, 128.9, 127.7, 109.1, 81.7, 64.7, 64.4, 50.7, 48.0, 42.2, 31.9, 28.5, 28.1, 27.2, 25.1, 23.0, 22.7, 22.2, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{43}N_2O_3$ 443.32682, found 443.32668.

(*R*)-*tert*-Butyl 2-[(2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-3-(3-chloro-3-phenylprop-1-en-2-yl)octanamido]-4-methylpentanoate (22). Prepared from **19** following the same desilylation/chlorination sequence described for the **14** → **16** reaction.

Data for the primary alcohol intermediate (93%): $[\alpha]^{24}_D$ +4.1 (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 7.21 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 5.26 (d, *J* = 9.0 Hz, 1H), 4.44 (m, 2H), 4.26 (m, 2H), 3.98 (s, 1H), 2.63 (t, *J* = 8.0 Hz, 1H), 2.03 (s, 1H), 1.71−1.47 (m, 3H), 1.43 (m, 11H), 1.35 (s, 9H), 1.32−1.09 (m, 6H), 0.94−0.80 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.7, 156.1, 139.0, 136.7, 132.7, 129.1, 128.2, 127.1, 82.2, 80.2, 60.2, 58.4, 51.4, 49.7, 42.0, 34.8, 31.9, 29.3, 28.4, 28.1, 28.0, 27.1, 25.4, 24.9, 22.9, 22.7, 22.1, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{53}N_2O_6$ 561.39037, found 561.38930.

Data for the diastereomeric mixture of allylic chlorides **22** (84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.18 (m, 6H), 6.23 (d, *J* = 8.6 Hz, 0.5H), 6.02 (d, *J* = 8.2 Hz, 0.5H), 5.50 (s, 0.5H), 5.38 (s, 0.5H), 5.18 (m, 0.5H), 5.05 (s, 0.5H), 4.85 (m, 1H), 4.63−4.45 (m, 2H), 2.99 (m, 1H), 1.73 (m, 0.5H), 1.63−1.48 (m, 3H), 1.46 (m, 9.5H), 1.40 (m, 6H), 1.34−1.18 (m, 4H), 1.12 (m, 5H), 0.94 (m, 6H), 0.85 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.0, 169.8, 169.6, 154.3, 152.6, 151.0, 144.5, 142.7, 128.91, 128.88, 128.7, 128.6, 128.4, 127.3, 127.0, 125.2, 124.9, 106.7, 106.2, 82.2, 81.9, 80.9, 80.3, 67.0, 66.5, 65.2, 64.1, 51.3, 51.2, 44.0, 43.7, 42.9, 42.7, 32.3, 32.2, 28.4, 28.3, 28.2, 28.1, 28.04, 28.00, 26.6, 26.3, 25.0, 24.7, 23.1, 22.8, 22.6, 22.5, 22.3, 22.2, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{52}ClN_2O_5$ 579.35593, found 579.35374; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{32}H_{51}ClN_2O_5Na$ 601.33787, found 601.33532.

(*R*)-*tert*-Butyl 4-Methyl-2-[(2*S*,3*R*,5*R*)-4-methylene-3-pentyl-5-phenylpyrrolidine-2-carboxamido]pentanoate (23). Prepared from **22** following the same deprotection/cyclization procedure described for the **14** → **16** reaction (59%): $[\alpha]^{26}_D$ −7.4 (*c* 1.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.0 Hz, 1H), 7.33 (m, 2H), 7.26 (m, 3H), 4.98 (d, *J* = 1.3 Hz, 1H), 4.82 (s, 1H), 4.56 (m, 2H), 4.21 (d, *J* = 6.8 Hz, 1H), 2.95 (m, 1H), 1.70 (m, 1H), 1.65−1.50 (m, 2H), 1.43 (m, 12H), 1.37−1.20 (m, 5H), 0.93 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 172.1, 154.8, 144.5, 128.9, 127.7, 127.6, 109.4, 81.9, 64.7, 64.5, 50.8, 47.7, 42.0, 32.0, 29.0, 28.1, 27.1, 25.1, 23.1, 22.7, 22.0, 14.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{43}N_2O_3$ 443.32682, found 443.32647.

(*S*)-*tert*-Butyl 2-{(2*R*,3*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylhex-4-enamido}-4-methylpentanoate (25). A solution of **24** (260 mg, 0.508 mmol) in 3.5 mL of MeCN was treated with HBTU (250 mg, 0.661 mmol), HOBt (13.7 mg, 0.102 mmol), NEt_3 (354 μL, 2.54 mmol), and H-Leu-O*t*Bu-HCl (136 mg, 0.609 mmol). After being stirred at rt for 20 h, the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with 1 M aq HCl followed by 10% aq Na_2CO_3. The organic layer was dried over Na_2SO_4 and evaporated. Purification by flash column chromatography over silica gel (10−20% EtOAc/hexanes) afforded **25** as a white foam (268 mg, 77%): $[\alpha]^{24}_D$ −10.3 (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.62 (m, 4H), 7.49−7.32 (m, 6H), 6.32 (d, *J* = 8.3 Hz, 1H), 5.38−5.14 (m, 2H), 4.49 (m, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.21 (d, *J* = 12.4 Hz, 1H), 3.08 (m, 1H), 1.68−1.50 (m, 2H), 1.44 (m, 10H), 1.38 (m, 12H), 1.11−1.03 (m, 12H), 0.95−0.86 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.2, 155.7, 139.2, 135.8, 135.7, 133.5, 133.4, 129.8, 129.8, 127.9, 127.8, 127.7, 122.8, 81.8, 60.8, 57.5, 51.2, 41.9, 39.3, 28.4, 28.1, 27.1, 24.9, 22.9, 22.0, 19.4, 13.3; HRMS (ESI-TOF) m/z $[MH]^+$ calcd for $C_{39}H_{61}N_2O_6Si$ 681.42989, found 681.43066.

(*S*)-*tert*-Butyl 2-[(2*R*,3*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-(hydroxymethyl)-3-methylhex-4-enamido]-4-methylpentanoate (26). Prepared from **25** following the same three-step procedure described for the **14** → **16** reaction.

Data for the allylic alcohol intermediate (90%): $[\alpha]^{24}_D$ −12.3 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 7.8 Hz, 1H), 5.44 (q, *J* = 6.8 Hz, 1H), 5.34 (d, *J* = 8.4 Hz, 1H), 4.48−4.29 (m, 3H), 4.11 (d, *J* = 11.3 Hz, 1H), 3.55 (bs, 1H), 2.63 (m, 1H), 2.10 (bs, 1H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.63−1.46 (m, 2H), 1.44 (m, 10H), 1.41 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.92 (dd, *J* = 6.3, 5.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.3, 156.2, 139.3, 125.6, 82.0, 80.2, 77.5, 76.8, 59.9, 57.6, 51.5, 43.1, 42.0, 28.4, 28.1, 25.0, 22.9, 22.1, 15.2, 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{43}N_2O_6$ 443.31156, found 443.31136.

Data for the intermediate allylic chloride (97%): $[\alpha]^{24}_D$ −27.9 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43−6.32 (m, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 4.99 (bs, 1H), 4.52−4.40 (m, 1H), 4.31−4.21 (m, 2H), 4.12 (d, *J* = 11.5 Hz, 1H), 2.93−2.81 (m, 1H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.68−1.46 (m, 3H), 1.44 (s, 9H), 1.40 (s, 9H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.92 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 170.8, 155.8, 137.0, 127.9, 82.1, 80.0, 57.1, 51.4, 42.0, 41.4, 41.2, 28.4, 28.1, 25.0, 22.9, 22.1, 14.3, 13.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{42}ClN_2O_5$ 461.27768, found 461.27780.

Data for **26** (70%, two steps): $[\alpha]^{24}_D$ −22.0 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (bs, 1H), 5.31 (m, 1H), 4.59 (bs, 1H), 4.42 (dd, *J* = 14.9, 7.5 Hz, 1H), 4.08 (d, *J* = 6.6 Hz, 1H), 3.87 (d, *J* = 14.5 Hz, 1H), 3.65 (d, *J* = 14.4 Hz, 1H), 2.92 (m, 1H), 1.72−1.59 (m, 1H), 1.55 (m, 5H), 1.42 (m, 9H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.91 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 169.4, 139.9, 116.7, 82.5, 64.0, 51.5, 47.2, 41.0, 40.0, 28.0, 25.9, 22.9, 21.7, 14.7, 14.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{33}N_2O_3$ 325.24857, found 325.25005.

(*S*)-2-{(2*R*,3*S*,*Z*)-1-[(*S*)-2-Benzamido-6-guanidinohexanoyl]-4-ethylidene-3-methylpyrrolidine-2-carboxamido}-4-methylpentanoic Acid (27). To a solution of **26** (70.0 mg, 0.215 mmol) and Fmoc-Har(Boc)$_2$-OH (158 mg, 0.259 mmol) in 3 mL of THF at 0 °C were added DEPBT (96.5 mg, 0.322 mmol) and NEt_3 (60.0 μL, 0.431 mol). The mixture was stirred at 0 °C for 6 h, the reaction quenched with saturated aq NH_4Cl, and the THF removed under reduced pressure. The crude residue was taken up in EtOAc and washed with 1 M HCl and saturated aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography over silica gel (30% EtOAc/hexanes) gave the desired tripeptide as a sticky white foam (148 mg, 75%): $[\alpha]^{24}_D$ +2.8 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (d, *J* = 5.9 Hz, 1H), 8.30 (m, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 7.0, 4.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 6.35 − 6.27 (m, 1H), 5.67 (d, *J* = 7.6 Hz, 1H), 5.39−5.26 (m, 1H), 4.62−4.32 (m, 5H), 4.31−4.02 (m, 3H), 3.45−3.33 (m, 2H), 3.03−2.83 (m, 1H), 1.89−1.75 (m, 1H), 1.75−1.54 (m, 5H), 1.52−1.37 (m, 33H), 1.18−1.06 (m, 3H), 0.96−0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotomers) δ 171.8, 170.9, 168.7, 163.7, 156.3, 156.2, 153.4, 144.0, 143.9, 141.4, 138.3, 127.8, 127.22, 127.18, 125.3, 120.1, 116.6, 83.2, 81.8, 79.4, 79.2, 67.3, 64.1, 52.4, 51.4, 49.1, 47.3, 41.8, 40.7, 38.8, 32.5, 29.0, 28.44, 28.42, 28.2, 28.09, 28.05, 25.2, 24.9, 22.7, 22.3, 14.7, 12.2, 11.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{50}H_{73}N_6O_{10}$ 917.53882, found 917.53804.

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The tripeptide described above (80.0 mg, 87.2 μmol) in 2 mL of THF was treated with diethylamine (0.362 mL, 3.49 mmol) and stirred for 5 h at rt. The mixture was evaporated under reduced pressure. The crude was dissolved in 1.5 mL of CH_2Cl_2 and treated with benzoyl chloride (20.0 μL, 0.174 mmol). After 1.5 h, the mixture was concentrated. The crude was adsorbed onto silica gel and purified by flash column chromatography over silica gel (50% EtOAc/hexanes and then 10% MeOH/EtOAc) to give the benzoyl tripeptide as a white foam (61.0 mg, 87%, two steps): $[\alpha]^{24}_D$ +6.8 (*c* 2.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (bs, 1H), 8.30 (m, 1H), 8.07 (m, 1H), 7.81 (m, 2H), 7.50−7.35 (m, 3H), 7.19 (dd, *J* = 22.7, 8.0 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.43−5.24 (m, 1H), 5.12−4.93 (m, 0.5H), 4.86 (q, *J* = 7.0 Hz, 0.5H), 4.76 (d, *J* = 13.9 Hz, 1H), 4.58 (d, *J* = 8.9 Hz, 1H), 4.38 (m, 1H), 4.32−4.17 (m, 1H), 3.46−3.32 (m, 2H), 2.95 (m, 1H), 2.00−1.76 (m, 2H), 1.73−1.55 (m, 4H), 1.54−1.34 (m, 32H), 1.19−1.08 (m, 3H), 0.98−0.89 (m, 2H), 0.78 (d, *J* = 6.3 Hz, 2H), 0.66 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.7, 171.3, 171.0, 169.7, 168.7, 167.7, 167.5, 163.6, 163.7, 156.3, 156.2, 153.4, 153.3, 138.2, 137.8, 133.7, 133.6, 133.1, 132.0, 131.9, 130.1, 128.7, 128.6, 128.4, 127.4, 116.8, 116.0, 83.2, 83.0, 81.8, 81.5, 79.4, 79.2, 64.7, 64.3, 51.5, 51.4, 51.0, 49.3, 49.2, 41.4, 40.9, 40.6, 40.6, 38.9, 32.1, 32.0, 29.0, 28.4, 28.2, 28.1, 28.0, 25.2, 24.7, 23.0, 22.9, 22.8, 22.6, 22.1, 22.0, 14.7, 14.6, 12.2, 12.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{42}H_{67}N_6O_9$ 799.49696, found 799.49680.

The benzoylated tripeptide mentioned above (30.0 mg, 37.5 μmol) was treated with 3 mL of a TFA/TES/CH_2Cl_2 solution (90:5:5) at rt and stirred for 8.5 h. The mixture was diluted with EtOAc and evaporated under reduced pressure. The dilution and evaporation were repeated two more times. The crude was purified by semipreparative RP-HPLC (20−60% MeCN/H_2O linear gradient over 30 min, retention time of 9.3 min) to afford **27** as a white solid (19.0 mg, 93%): $[\alpha]^{24}_D$ +18.1 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.60 (d, *J* = 7.1 Hz, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 7.92 (m, 2H), 7.57−7.43 (m, 3H), 6.89 (bs, 2H), 5.18 (m, 1H), 5.10 (m, 1H), 4.61 (m, 1H), 4.11−3.92 (m, 3H), 3.07 (m, 1H), 2.97 (m, 1H), 2.86 (m, 1H), 1.75−1.28 (m, 12H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.9, 170.8, 168.5, 166.5, 157.5, 139.9, 133.8, 131.4, 128.3, 127.6, 113.2, 63.8, 52.4, 51.5, 49.1, 41.6, 40.4, 30.6, 28.3, 24.6, 23.2, 22.7, 21.7, 14.2, 12.3; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{43}N_6O_5$ 543.32894, found 543.32673.

(*Z*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]pent-3-en-2-yl 2-(*tert*-Butoxycarbonylamino)acetate (30). Prepared according to the three-step procedure described for the **10a** → **11a** reaction (58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.62 (m, 4H), 7.45−7.32 (m, 6H), 5.80 (q, *J* = 6.7 Hz, 1H), 5.71 (q, *J* = 7.1 Hz, 1H), 4.90 (m, 1H), 4.21 (m, 1H), 4.11 (m, 1H), 3.83 (dd, *J* = 18.2, 5.8 Hz, 1H), 3.67 (dd, *J* = 18.3, 5.2 Hz, 1H), 1.73 (dt, *J* = 7.1, 1.3 Hz, 3H), 1.42 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.06 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 155.8, 137.1, 135.8, 135.7, 133.8, 133.7, 130.0, 129.9, 127.9, 127.8, 123.6, 80.1, 69.8, 64.2, 42.6, 28.5, 27.0, 19.5, 19.5, 13.2; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{42}NO_5Si$ 512.28268, found 512.28215.

(2*S,3*S**,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylhex-4-enoic Acid (31).** Prepared from **30** following the same procedure described for the **11a** → **13a** reaction (78%). Spectral data given for the mixture of rotamers and diastereomers (>95:5 dr): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.65 (m, 4H), 7.49−7.31 (m, 6H), 5.90 (d, *J* = 6.9 Hz, 1H), 5.53 (q, *J* = 6.7 Hz, 1H), 4.31 (t, *J* = 7.2 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 4.04 (d, *J* = 11.6 Hz, 1H), 2.88 (m, 1H), 1.43 (d, *J* = 7.5 Hz, 1H), 1.38 (m, 9H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.10−1.03 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 156.3, 138.1, 136.0, 135.9, 133.2, 133.0, 130.1, 130.0, 128.0, 127.7, 126.3, 80.1, 60.4, 58.9, 40.4, 28.6, 28.5, 27.2, 19.4, 17.4, 13.5; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{42}NO_5Si$ 512.28268, found 512.28213; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{41}NO_5SiNa$ 534.26462, found 534.26382.

(*S*)-*tert*-Butyl 2-{(2*R*,3*R*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylhex-4-enamido}-4-methylpentanoate (32) and (*S*)-*tert*-Butyl 2-{(2*S*,3*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)-4-[(*tert*-butyldiphenylsilyloxy)methyl]-3-methylhex-4-enamido}-4-methylpentanoate (33). Prepared from racemic **31** following the same procedure described for the **13a** → **14/15** reaction. Careful flash chromatography over silica gel afforded the diastereomeric dipeptides in 76% combined yield.

Data for **32** (37%): $[\alpha]^{24}_D$ +0.3 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.65 (m, 4H), 7.48−7.33 (m, 6H), 6.58 (dd, *J* = 30.1, 7.6 Hz, 1H), 5.92 (dd, *J* = 19.7, 5.8 Hz, 1H), 5.49 (q, *J* = 6.7 Hz, 1H), 4.44 (td, *J* = 8.7, 5.6 Hz, 1H), 4.30−4.22 (m, 1H), 4.15 (t, *J* = 6.6 Hz, 1H), 4.05 (dd, *J* = 11.5, 4.7 Hz, 1H), 2.87 (m, 1H), 1.72− 1.49 (m, 2H), 1.44 (m, 13H), 1.38 (s, 9H), 1.12−1.04 (m, 12H), 0.92 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 171.0, 155.8, 138.8, 136.0, 135.8, 133.2, 133.0, 130.0, 129.9, 127.9, 127.8, 125.4, 81.5, 79.6, 61.1, 59.3, 51.5, 41.6, 40.2, 28.4, 28.1, 27.2, 24.9, 22.9, 22.0, 19.3, 16.9, 13.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{39}H_{61}N_2O_6Si$ 681.42990, found 681.43009.

Data for **33** (39%): $[\alpha]^{24}_D$ −11.0 (*c* 1.00 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.66 (m, 4H), 7.50−7.32 (m, 6H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 6.4 Hz, 1H), 5.50 (m, 1H), 4.48 (td, *J* = 8.4, 5.9 Hz, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.13 (t, *J* = 7.2 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 1H), 2.88 (m, 1H), 1.67−1.48 (m, 2H), 1.42 (m, 13H), 1.36 (s, 9H), 1.11−1.00 (m, 12H), 0.97−0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.0, 156.0, 138.6, 136.1, 135.9, 133.4, 133.1, 130.1, 130.0, 128.0, 127.9, 125.9, 81.7, 79.6, 61.2, 59.2, 51.5, 42.2, 40.3, 28.5, 28.2, 27.3, 27.2, 24.9, 23.0, 22.4, 19.4, 16.8, 13.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{39}H_{61}N_2O_6Si$ 681.42990, found 681.43060.

(*S*)-*tert*-Butyl 2-[(2*R*,3*R*,*Z*)-4-Ethylidene-3-methylpyrrolidine-2-carboxamido]-4-methylpentanoate (34). Prepared from **32** following the same three-step procedure described for the **14** → **16** reaction.

Data for the primary alcohol intermediate (89%): $[\alpha]^{24}_D$ −11.3 (*c* 1.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.3 Hz, 1H), 6.01 (d, *J* = 8.6 Hz, 1H), 5.48 (q, *J* = 6.7 Hz, 1H), 4.43 (m, 1H), 4.35 (dd, *J* = 8.6, 5.5 Hz, 1H), 4.24 (dd, *J* = 31.4, 12.0 Hz, 1H), 4.14−3.99 (m, 1H), 3.69 (m, 1H), 2.86 (m, 1H), 2.13 (bs, 1H), 1.70−1.51 (m, 5H), 1.50−1.36 (m, 19H), 1.06 (m, 3H), 0.90 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 170.9, 156.2, 138.0, 127.6, 82.3, 80.0, 58.3, 57.9, 51.4, 43.4, 41.5, 28.5, 28.2, 25.1, 23.1, 21.9, 15.0, 13.5; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{43}N_2O_6$ 443.31156, found 443.31154.

Data for the allylic chloride intermediate (87%): $[\alpha]^{24}_D$ −41.9 (*c* 1.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 51.4, 7.3 Hz, 1H), 5.63 (q, *J* = 6.8 Hz, 1H), 5.30 (m, 1H), 4.43 (m, 1H), 4.17 (m, 3H), 2.88−2.68 (m, 1H), 1.76 (dd, *J* = 7.9, 7.3 Hz, 3H), 1.69−1.49 (m, 3H), 1.48−1.36 (m, 19H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.92 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 169.9, 155.5, 136.8, 129.7, 82.0, 80.0, 57.2, 51.7, 42.7, 42.0, 28.5, 28.2, 25.1, 23.0, 22.1, 15.4, 13.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{42}ClN_2O_5$ 461.27768, found 461.27766.

Data for pyrrolidine **34** (65%, two steps): $[\alpha]^{24}_D$ +17.8 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.6 Hz, 1H), 5.24 (m, 1H), 4.47 (td, *J* = 9.0, 5.0 Hz, 1H), 3.64 (m, 2H), 3.24 (d, *J* = 7.5 Hz, 1H), 2.63 (m, 1H), 2.05 (bs, 1H), 1.72−1.49 (m, 5H), 1.46−1.40 (m, 10H), 1.19 (d, *J* = 6.8, 3H), 0.93 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 172.3, 144.2, 114.5, 81.7, 68.6, 51.0, 48.1, 43.0, 42.0, 28.2, 28.2, 25.2, 23.1, 22.2, 18.0, 14.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}N_2O_3$ 325.24857, found 325.24875.

(*S*)-2-{(2*R*,3*R*,*Z*)-1-[(*S*)-2-Benzamido-6-guanidinohexanoyl]-4-ethylidene-3-methylpyrrolidine-2-carboxamido}-4-methylpentanoic Acid (35). Prepared from **16** according the same three-step procedure described for the **26** → **27** reaction.

Data for the Fmoc-Har(Boc)$_2$-Emp-Leu-O*t*Bu intermediate (77%): $[\alpha]^{24}_D$ +19.6 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 8.32 (t, *J* = 4.2 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 15.9, 8.4 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 1H), 5.70 (d, *J* = 7.5 Hz, 1H), 5.43 (m, 1H), 4.52−4.29 (m, 5H), 4.29−4.15 (m, 3H), 3.42 (dd, *J* = 12.5, 6.8 Hz, 2H), 3.15 (m, 1H), 1.90−1.69 (m, 1H), 1.69−1.54 (m, 5H), 1.52−1.42 (m, 24H), 1.37 (s, 9H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.9 (m, 6H); ^{13}C NMR

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(101 MHz, $CDCl_3$) δ 172.0, 170.0, 163.7, 156.4, 156.3, 153.4, 143.9, 141.4, 139.1, 127.9, 127.3, 127.2, 125.3, 120.1, 118.2, 83.3, 81.6, 79.4, 77.5, 76.8, 67.4, 66.6, 52.7, 51.4, 47.8, 47.2, 41.7, 40.7, 40.6, 32.2, 29.1, 28.4, 28.2, 28.0, 24.9, 23.0, 22.1, 21.3, 14.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{50}H_{73}N_6O_{10}$ 917.53882, found 917.53662.

Data for the *N*-benzoyl tripeptide intermediate (79%): $[\alpha]^{24}_D$ +33.9 (c 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (bs, 1H), 8.32 (m, 1H), 8.06 (m, 1H), 7.81 (m, 2H), 7.47 (m, 1H), 7.41 (q, J = 7.1 Hz, 2H), 7.11 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 6.9 Hz, 1H), 5.45 (m, 1H), 4.84 (q, J = 7.0 Hz, 1H), 4.51 (d, J = 14.4 Hz, 1H), 4.43 (td, J = 8.9, 5.1 Hz, 1H), 4.37 (d, J = 1.8 Hz, 1H), 4.30 (d, J = 14.4 Hz, 1H), 3.40 (m, 2H), 3.14 (m, 2H), 2.03−1.77 (m, 2H), 1.74−1.56 (m, 5H), 1.51−1.41 (m, 23H), 1.36 (s, 9H), 1.17 (d, J = 7.2 Hz, 3H), 0.82 (d, J = 6.0 Hz, 3H), 0.69 (d, J = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.9, 169.9, 167.7, 163.7, 156.3, 153.4, 139.0, 133.4, 133.2, 132.0, 130.1, 128.6, 128.5, 127.4, 118.3, 83.3, 81.4, 79.4, 77.5, 76.8, 66.8, 51.9, 51.4, 48.0, 41.3, 41.2, 40.6, 31.8, 29.1, 28.4, 28.2, 28.0, 24.7, 23.1, 22.8, 21.9, 21.4, 14.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{42}H_{67}N_6O_9$ 799.49696, found 799.49690.

Data for **35** (78%): $[\alpha]^{24}_D$ +22.4 (c 0.50, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.66 (d, J = 7.1 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.90 (m, 2H), 7.53 (m, 1H), 7.45 (m, 2H), 6.99 (bs, 1H), 5.26 (dd, J = 13.6, 10.9 Hz, 1H), 4.70 (d, J = 2.0 Hz, 1H), 4.45 (m, 1H), 4.17 (d, J = 16.0 Hz, 1H), 4.01 (dt, J = 9.9, 3.8 Hz, 1H), 3.89 (d, J = 16.9 Hz, 1H), 3.06 (m, 1H), 2.93 (m, 1H), 2.63 (q, J = 6.6 Hz, 1H), 1.75−1.27 (m, 12H), 1.17 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.1 Hz, 3H), 0.80 (d, J = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.0, 171.3, 170.6, 166.4, 157.6, 140.4, 133.8, 131.3, 128.2, 127.6, 115.1, 66.6, 52.3, 51.5, 48.0, 45.2, 41.3, 40.7, 30.1, 28.1, 24.9, 23.3, 21.6, 21.3, 14.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{43}N_6O_5$ 543.32894, found 543.32675.

(*S*)-*tert*-Butyl 2-[(2*S*,3*S*,*Z*)-4-Ethylidene-3-methylpyrrolidine-2-carboxamido]-4-methylpentanoate (36). Prepared from **33** following the same three-step procedure described for the **14** → **16** reaction.

Data for the primary alcohol intermediate (92%): $[\alpha]^{24}_D$ −11.3 (c 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J = 7.8 Hz, 1H), 5.62 (d, J = 8.3 Hz, 1H), 5.48 (q, J = 6.8 Hz, 1H), 4.39 (td, J = 8.3, 5.9 Hz, 1H), 4.26 (m, 2H), 4.18 (m, 1H), 3.70 (t, J = 5.1 Hz, 1H), 2.60 (m, 1H), 1.66 (d, J = 6.9 Hz, 3H), 1.64−1.50 (m, 1H), 1.47 (m, 1H), 1.44−1.34 (m, 20H), 1.06 (d, J = 7.0 Hz, 3H), 0.89 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 170.6, 156.2, 138.5, 126.7, 82.0, 80.1, 58.8, 57.8, 51.8, 44.0, 42.0, 28.5, 28.2, 25.0, 22.9, 22.3, 14.5, 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{43}N_2O_6$ 443.31156, found 443.31124.

Data for the allylic chloride intermediate (94%): $[\alpha]^{24}_D$ +26.8 (c 1.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, J = 7.8 Hz, 1H), 5.72 (q, J = 6.9 Hz, 1H), 5.33 (d, J = 7.3 Hz, 1H), 4.42 (td, J = 8.5, 5.5 Hz, 1H), 4.29−4.15 (m, 2H), 4.10 (d, J = 11.3 Hz, 1H), 2.72 (m, 1H), 1.79 (dd, J = 7.3, 3.5 Hz, 3H), 1.68−1.51 (m, 2H), 1.50−1.37 (m, 19H), 1.07 (d, J = 7.0 Hz, 3H), 0.91 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.0, 155.6, 136.5, 130.4, 81.9, 79.9, 57.1, 51.8, 43.1, 42.0, 41.8, 28.5, 28.2, 25.0, 23.0, 22.3, 15.3, 13.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{42}ClN_2O_5$ 461.27768, found 461.27776.

Data for pyrrolidine **36** (64%, two steps): $[\alpha]^{24}_D$ −39.4 (c 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.6 Hz, 1H), 5.26 (m, 1H), 4.47 (td, J = 8.9, 5.0 Hz, 1H), 3.64 (m, 2H), 3.25 (d, J = 7.5 Hz, 1H), 2.56 (m, 1H), 2.37−2.17 (m, 1H), 1.68−1.49 (m, 5H), 1.45 (m, 10H), 1.21 (m, 3H), 0.92 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 172.5, 143.9, 114.8, 81.9, 68.5, 51.0, 47.9, 43.6, 42.0, 28.2, 28.1, 25.2, 23.1, 22.2, 17.9, 14.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{33}N_2O_3$ 325.24857, found 325.24865.

(*S*)-2-{(2*S*,3*S*,*Z*)-1-[(*S*)-2-Benzamido-6-guanidinohexanoyl]-4-ethylidene-3-methylpyrrolidine-2-carboxamido}-4-methylpentanoic Acid (37). Prepared from **37** according the same three-step procedure described for the **26** → **27** reaction.

Data for the Fmoc-Har(Boc)$_2$-Emp-Leu-O*t*Bu intermediate (77%): $[\alpha]^{24}_D$ −8.5 (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 8.34 (t, J = 4.9 Hz, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 6.52 (d, J = 8.1 Hz, 1H), 5.65 (d, J = 8.7 Hz, 1H), 5.41 (m, 1H), 4.57 (td, J = 8.6, 4.7 Hz, 1H), 4.51−4.27 (m, 3H), 4.26−4.03 (m, 3H), 3.43 (dd, J = 13.5, 7.1 Hz, 2H), 3.03 (m, 1H), 1.88−1.55 (m, 8H), 1.48 (m, 32H), 1.19 (m, 3H), 0.97−0.80 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 172.1, 170.1, 163.8, 156.3, 156.3, 153.4, 144.0, 143.9, 141.4, 139.3, 127.8, 127.2, 125.3, 125.3, 120.1, 117.6, 83.2, 82.0, 79.3, 67.2, 67.1, 52.3, 51.6, 48.4, 47.3, 42.0, 40.7, 40.6, 32.8, 31.7, 29.0, 28.5, 28.2, 28.1, 28.0, 25.0, 23.0, 22.8, 22.7, 22.4, 21.5, 19.7, 14.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{50}H_{73}N_6O_{10}$ 917.53882, found 917.54052.

Data for the *N*-benzoyl tripeptide intermediate (85%): $[\alpha]^{24}_D$ −3.2 (c 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (bs, 1H), 8.32 (d, J = 5.0 Hz, 1H), 8.07 (m, 1H), 7.80 (m, 2H), 7.59−7.32 (m, 5H), 7.25 (m, 1H), 6.55 (d, J = 8.2 Hz, 1H), 5.40 (m, 1H), 5.05 (td, J = 8.4, 4.8 Hz, 1H), 4.65 (dd, J = 23.8, 10.1 Hz, 1H), 4.46 (td, J = 8.4, 5.6 Hz, 1H), 4.24 (d, J = 14.1 Hz, 1H), 4.18 (d, J = 4.1 Hz, 1H), 3.41 (dd, J = 12.3, 6.8 Hz, 2H), 2.99 (m, 1H), 2.00−1.73 (m, 1H), 1.72−1.41 (m, 35H), 1.22−1.12 (m, 3H), 0.91 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 172.2, 170.2, 167.3, 163.7, 156.2, 153.4, 139.3, 133.9, 133.2, 131.8, 128.6, 128.5, 128.4, 127.4, 127.3, 117.6, 83.1, 82.0, 79.3, 67.2, 51.6, 50.8, 48.6, 42.0, 40.8, 40.7, 32.6, 29.0, 28.4, 28.2, 28.1, 28.0, 25.0, 22.9, 22.8, 22.3, 19.6, 14.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{42}H_{67}N_6O_9$ 799.49696, found 799.49590.

Data for **37** (84%, two steps): $[\alpha]^{24}_D$ −31.4 (c 0.67, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (bs, 1H), 8.59 (d, J = 6.7 Hz, 1H), 8.21 (s, 0.5H), 7.88 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.04 (d, J = 6.7 Hz, 2.5H), 5.35 (t, J = 16.2 Hz, 1H), 4.88−4.68 (m, 2H), 4.31 (d, J = 14.4 Hz, 1H), 3.96 (d, J = 3.1 Hz, 1H), 3.84 (q, J = 6.5 Hz, 1H), 3.18 (m, 1H), 3.03 (m, 1H), 2.73 (m, 1H), 2.02 (m, 1H), 1.79−1.24 (m, 12H), 1.09 (d, J = 6.9 Hz, 3H), 0.82 (dd, J = 6.4, 3.9 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.7, 171.5, 168.8, 166.1, 157.1, 139.9, 133.7, 131.4, 128.2, 127.5, 116.4, 67.6, 52.3, 51.1, 47.3, 42.6, 42.0, 41.0, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 31.5, 28.9, 24.4, 23.1, 22.9, 20.1, 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{28}H_{43}N_6O_5$ 543.32894, found 543.32763.

Cell Growth Inhibition Assay. Compounds **1**, **27**, **35**, and **38** were evaluated using a CellTiter-Blue cell viability assay with doxorubicin as a positive control. For the assays, 0.8−3 × 10^3 HCT-116 cells in a 24 μL volume were plated in 384-well plates and incubated overnight at 37 °C in 5% CO_2. The next day, the compounds were diluted in media, and 6 μL of these dilutions was added to the appropriate wells. Four replicate wells were used for each compound concentration, and four additional negative control wells received a diluent control without compounds. Compound dilutions consisted of 2-fold dilutions from a maximum final concentration of 100 μM. The cells were incubated with compounds for 72 h. At this time, 5 μL of CellTiter-Blue reagent (Promega Corp., Madison, WI) was added to each well. Cell viability was assessed by the ability of the remaining viable cells to bioreduce resazurin to resorufin. Resazurin is dark blue in color and has little intrinsic fluorescence until it is reduced to resorufin (excitation at 579 nm and emission at 584 nm). The change in fluoresence was measured with a Synergy 4 microplate reader (Bio-Tek Instruments, Inc., Winooski, VT). The fluorescence data were then transferred to a spreadsheet program to calculate the percent viability relative to the four replicate cell wells that did not receive compounds. The positive control, doxorubicin, exhibited an IC_{50} of 268 nM. Compunds **1**, **27**, **35**, and **38** did not inhibit cell viability more than 15% at the largest dose tested (100 μM).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds, X-ray structure data for **1**, and NMR comparison table for natural lucentamycin A and synthetic isomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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