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"Doubly Customizable" Unit for the Generation of Structural Diversity: From Pure Enantiomeric Amines to Peptide Derivatives

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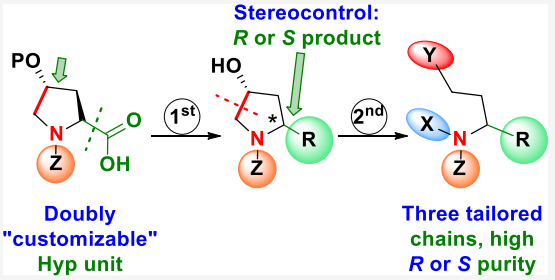
ABSTRACT: Readily available, low-cost 4*R*-hydroxy-L-proline (Hyp) is introduced as a "doubly customizable" unit for the generation of libraries of structurally diverse compounds. Hyp can be cleaved at two points, followed by the introduction of new functionalities. In the first cycle, the removal and replacement of the carboxylic group are carried out, followed (second cycle) by the scission of the 4,5-position and manipulation of the resulting chains. In this way, three new chains are generated and can be transformed independently to afford a diversity of products with tailored substituents, such as *β*-amino aldehydes, diamines, *β*-amino acid derivatives, including N-alkylated ones, or modified peptides. Many of these products are high-profit compounds but, in spite of their commercial value, are still scarce. Moreover, the process takes place with stereochemical control, and either pure *R* or *S* isomers can be obtained with small variations of the synthetic route.



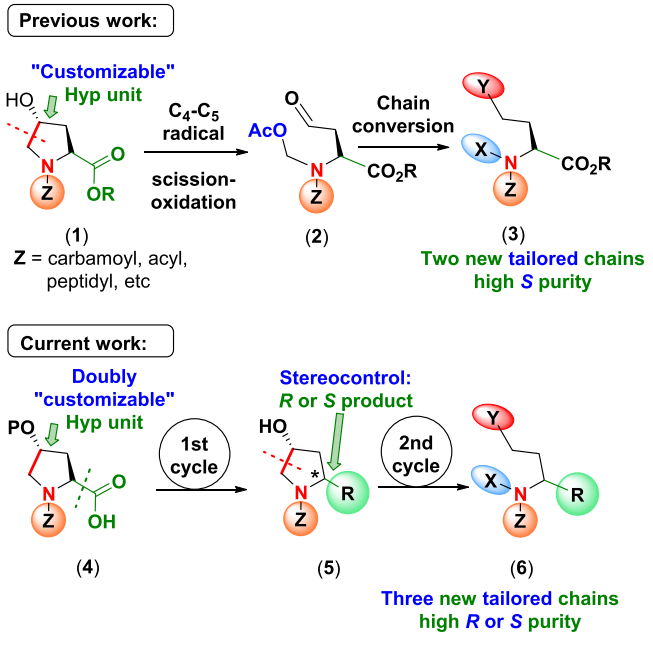
INTRODUCTION

"Customizable" amino acid units such as Hyp, Ser/Thr, or Glu have proven to be valuable for the conversion of readily available amino acids into a variety of nonproteinogenic residues or amino acid analogues.[1,2] In addition, these units allow the site-selective modification of peptides and the fast generation of peptide libraries.[3]

Customizable units undergo the cleavage of a certain functional group or C−C bond, followed by the introduction of novel groups such as acetoxy, amino, thioalkyl, phosphoryl, alkyl, or aryl, depending on the reaction conditions (Scheme 1).[1,2] We had previously introduced 4-hydroxyproline (Hyp) as a customizable unit, where the C_4−C_5 bond was cleaved using a domino radical scission−oxidation process (conversion **1** → **2**, Scheme 1), generating an *N*-acetoxymethyl 4-oxohomoalanine derivative with new N- and *α*-chains, which could be functionalized independently.[1,4] Resulting products **3** presented two new tailored chains and high *S* purity.

In the present paper, we report a Hyp-derived doubly customizable unit, where two different C−C bonds are cleaved sequentially, generating three new chains that can be manipulated separately (conversion **4** → **6**, Scheme 1). Moreover, both the nature and the stereochemistry of the resulting product can be tailored, by choosing the appropriate set of reaction conditions, affording an important structural diversity. Amines, diamines, amino acids, and amino acid analogues with either *R* or *S* configuration can be obtained from a single, low-cost L-Hyp unit. The application of this doubly customizable unit to generate branched peptides will also be highlighted.

Scheme 1. Introduction of the Doubly Customizable Hyp Unit



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RESULTS AND DISCUSSION

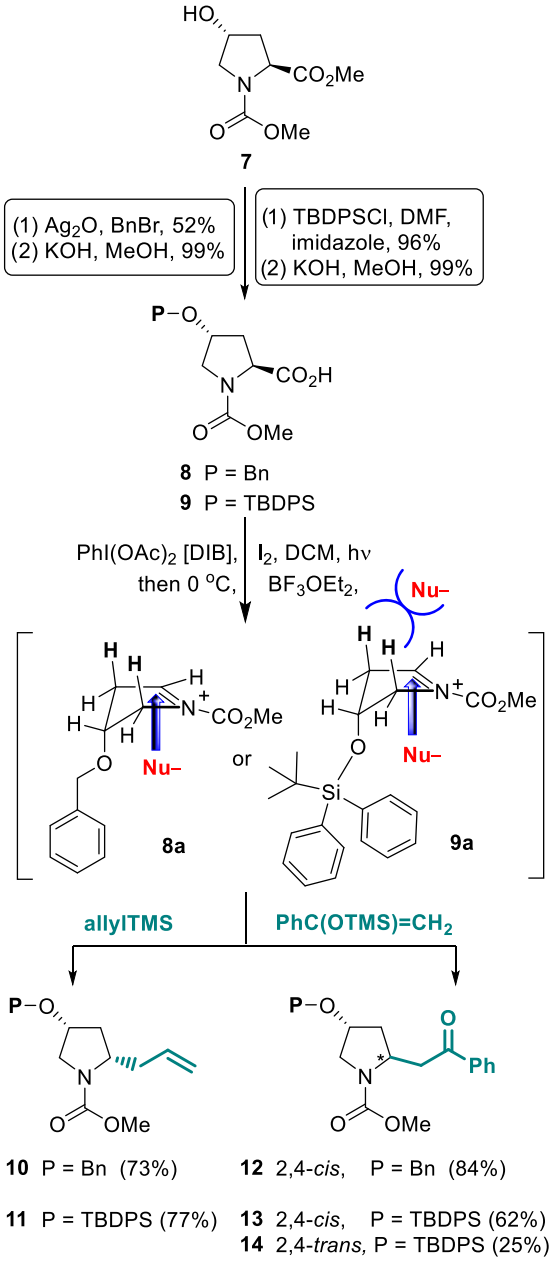
One-pot decarboxylation of the Hyp unit and introduction of a new chain at C-2 were studied first (Scheme 2). Natural 4*R*-hydroxyproline presents a stereogenic center at C-4, which could be used after decarboxylation for the stereocontrolled introduction of new chains on C-2. Two strategies were studied: in the first one, the role of the protecting group **P** in inducing *R* or *S* stereochemistry was explored. Readily available and removable groups were chosen, such as benzyl and silyl ethers. Thus, commercial hydroxyproline derivative **7** was transformed into benzyl ether **8** and bulky silyl ether **9** in good yields.[5] These substrates underwent radical decarboxylation−oxidation by treatment with (diacetoxyiodo)benzene (DIB) and iodine under irradiation with visible light, generating a 2-acetoxypyrrolidine (not shown).[6] This intermediate was treated in situ with a Lewis acid to generate an iminium ion (**8a** or **9a**), which was trapped by C-nucleophiles.[6,7] In the case of small nucleophile allyltrimethylsilane (allylTMS), both substrates were transformed into 2,4-cis products **10** and **11**. The prevalence of the cis product over the less hindered trans isomer[8] is due to a stereoelectronic effect described by Woerpel for 4-substituted five-membered cyclic iminium ions.[8a,b] Thus, when the substituent at C-4 is an oxygenated function, the iminium intermediate **8a** or **9a** adopts an envelop conformation, where axial H-groups hinder the introduction of nucleophiles from the face opposite to the OP group.

With bulkier nucleophiles, such as 1-phenyl-2-(trimethylsilyloxy)ethene, the ratio of 2,4-cis and trans isomers depended on the size of the protecting group P. Thus, for P = Bn, cis isomer **12** was obtained as the sole product, but for the much larger P = TBDPS, a separable cis/trans mixture **13:14** was obtained, in good global yield.

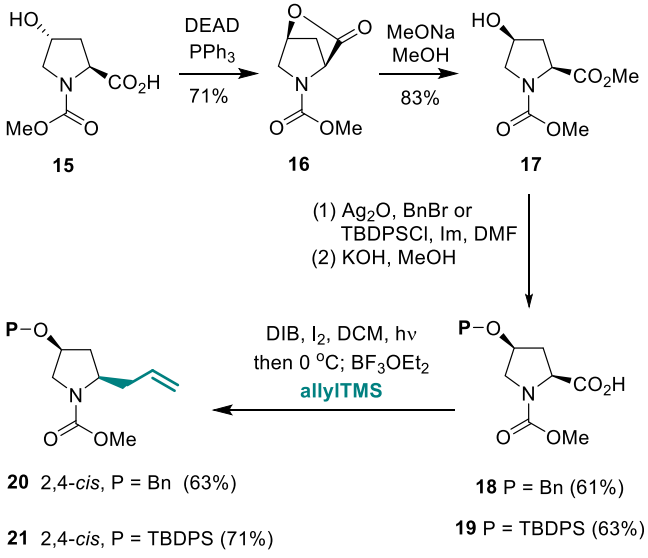
The previous major products (2,4-cis) had a 2*S* configuration for compounds **10** and **11** and a 2*R* configuration for products **12** and **13**. To obtain the other 2-isomers, a second approach was followed, where the inversion of the configuration at C-4 was carried out readily (conversion **15** → **16**, Scheme 3) by an intramolecular Mitsunobo reaction, followed by cleavage of the strained ring to afford ester **17**.[9] The preparation of benzyl ether **18** and silyl enol ether **19** was carried out as before,[5,10] and then the one-pot radical scission−oxidation−alkylation was studied. To our satisfaction, the stereochemistry of the new substrate did not favor side reactions, and the scission proceeded readily. The nucleophile allylTMS was added, giving similar results as before. New products **20**/**21** are again 2,4-*cis* (no 2,4-trans compounds were observed), but the 2*R* isomers were obtained instead.

With the possibility to obtain either 2*R* or 2*S* isomers, the introduction of different nucleophiles was studied using the less bulky *tert*-butyldimethylsilyl (TBS) ether **22** as the substrate (Scheme 4).[10] The sequential radical scission−oxidation−alkylation was carried out with allylTMS, PhC(OTMS)=CH_2, and the silyl ketene Me_2C=C(OTMS)OMe to afford products **23**−**26**. Interestingly, the two first nucleophiles afforded only the 2,4-cis product, but the ketene

Scheme 2. Influence of the Protecting Group P in the Stereochemical Outcome



Scheme 3. Prevalence of the Other 2-Isomers



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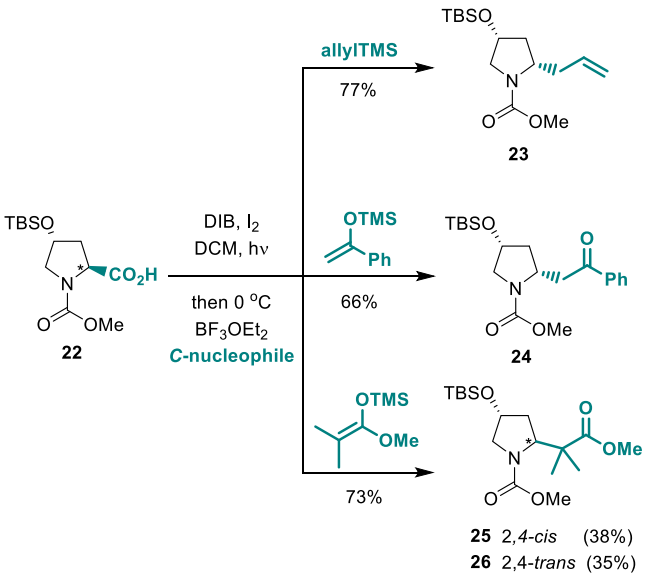
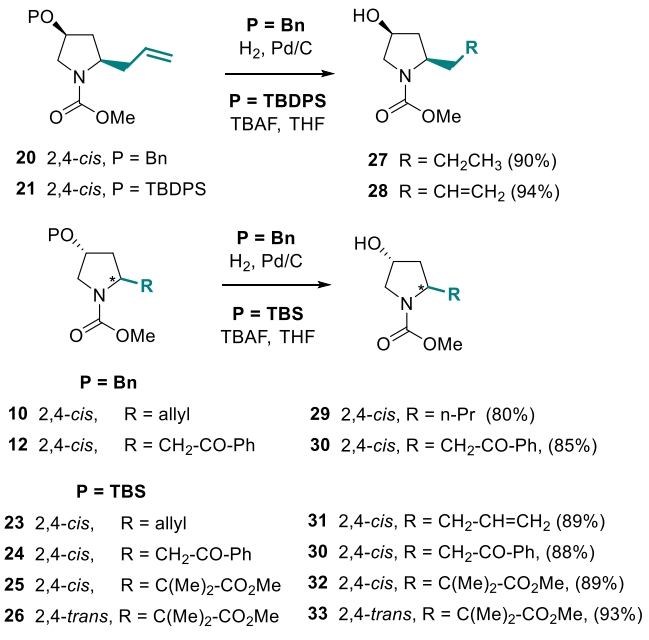
Scheme 4. Preparation of the Substrates for the Second Cycle of Transformations



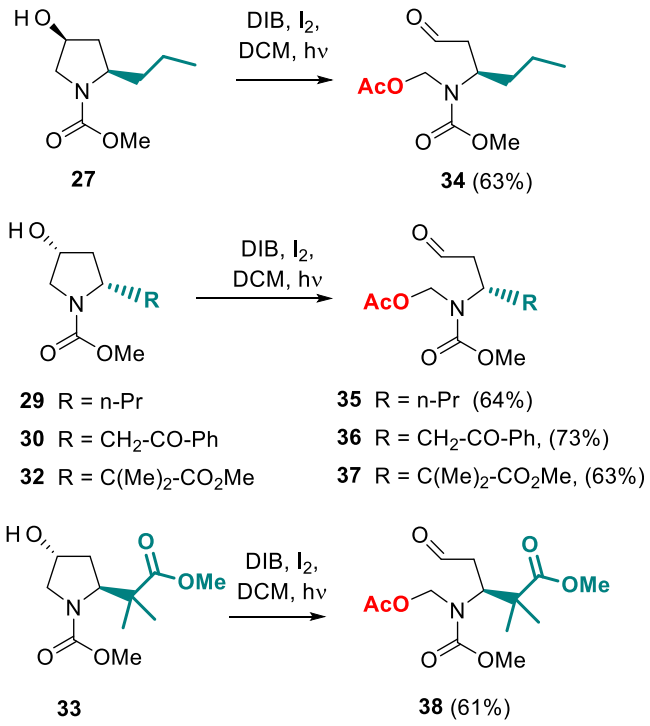
provided separable mixtures of the cis and trans isomers. This is due to the steric hindrance generated during the approach of this crowded, tetrasubstituted ketene to the iminium intermediate. It should be pointed out that β-amino acids, such as compounds **25** and **26**, are valuable reagents for the preparation of bioactive peptides with superior resistance to protease degradation[11] and also for the development of foldamers with tunable properties in material science.[12] This method readily affords β-units with the unusual D-stereochemistry (e.g. **25**), while the L-isomers could be obtained from substrate **17**.

The transformation of products **10**, **12**, **20**, **21**, and **23**–**26** into acyclic derivatives, by scission of the C_4–C_5 bond (second cycle of transformations), was studied next (Schemes 5 and 6).

Scheme 5. Removal of the Protecting Group to Provide Scission Substrates 27–33



Scheme 6. Second Cycle of Transformations to Give Acyclic β-Amino Aldehydes



The deprotection of the different hydroxy derivatives was carried out under different conditions, as shown in Scheme 5, providing the substrates for the second scission in good to excellent yields.

Then, substrates **27**, **29**, **30**, **32**, and **33** underwent the scission reaction to give *N*-acetoxymethyl derivatives **34**–**38** in good yields (Scheme 6).[4] These aldehydes (and related ones) can be readily oxidized using mild conditions[13] to afford different β-amino acids, which are valuable commercial products.

The aldehyde can also undergo reductive amination[4c] to give different chiral diamines, as illustrated with transformations **36** → **39** and **38** → **41** (Scheme 7). In the case of ketone **39**, the reaction proceeded selectively and the ketone was unaffected due to the higher reactivity of the aldehyde. As shown in the scheme, the reductive amination proceeds without affecting the *N*,*O*-acetal. Then, the acetal can be transformed independently (conversions **39** → **40** and **41** → **42**), adding diversity to the product libraries. It should be pointed out that the addition of allylTMS to substrate **39** proceeds chemoselectively, and only the *N*,*O*-acetal is transformed, while the ketone remains intact.

The ready introduction of an olefinic chain to the amine in product **40** is noteworthy since it can be used for ligation to other molecules.[14] Finally, the reduction of the *N*,*O*-acetal in **37** to a methyl group provided *N*-methyl β-amino ester **41**. Although *N*-alkyl β-amino acids are valuable components of foldamers, they are commercially scarce; this route could provide easy access to these compounds.

The reductive amination can be useful to generate many different δ-amino-substituted β-amino esters, with either L- or D-residues, as shown by conversions **37** → **43** and **38** → **44** (Scheme 8), where a morpholino group found in the antimicrobial Cobicistat was introduced.[15] In addition, the reductive amination can provide branched peptides[16a] with β-amino acid units[16b] (conversions **37** → **45** and **38** → **46**),

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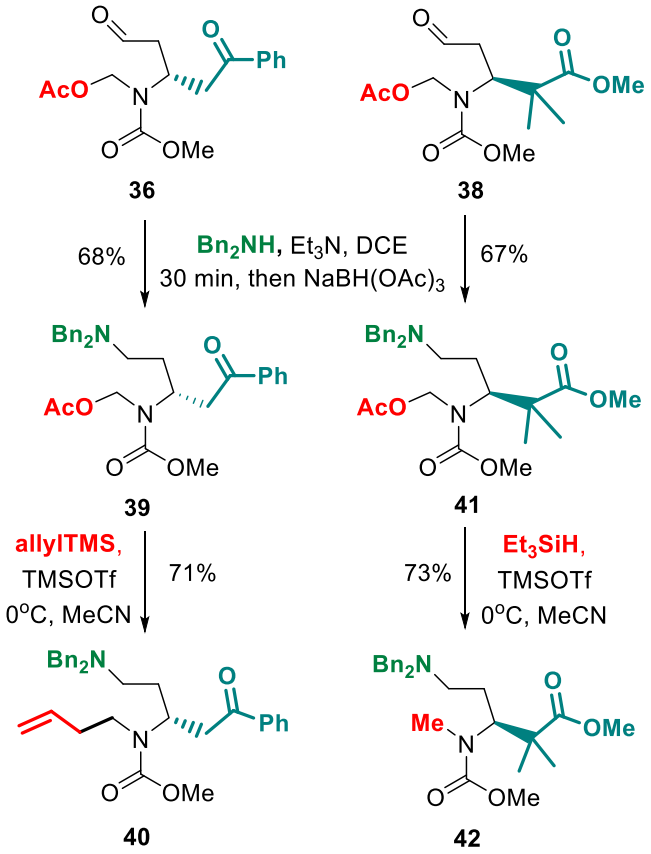
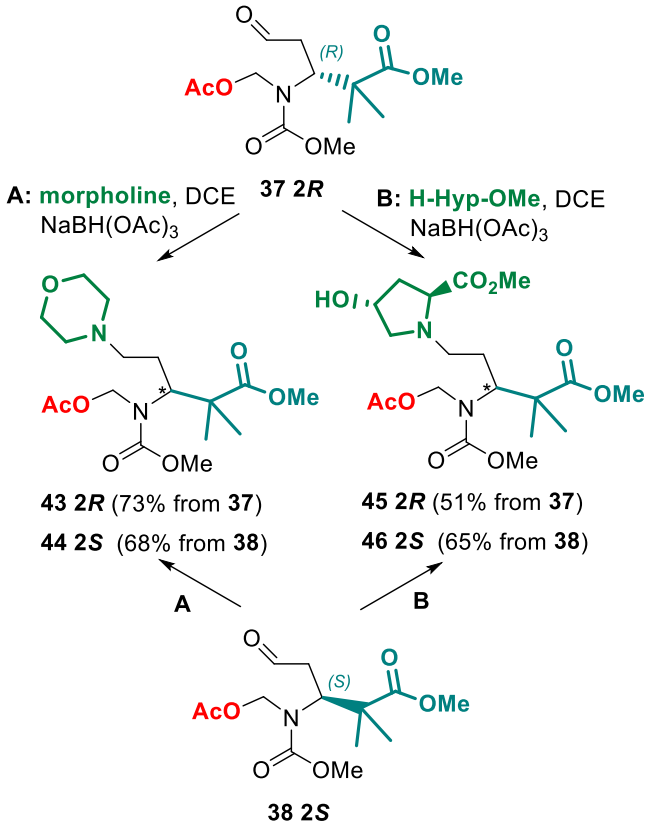
Scheme 7. Selective Functionalization of the Carbonylic Chain and the *N,O*-Acetal, Expanding Library Diversity



Scheme 8. Preparation of *β,δ*-Diamino Esters 43/44 and Branched Dipeptides 45/46



which could be components of functional materials or peptide drugs.

Finally, the *β*-amino aldehydes can also be functionalized with other reactions, as shown in Scheme 9 for the synthesis of peptides with a rigid dehydroamino acid unit.[17] The Horner−Wadsworth−Emmons (HWE) reaction of aldehydes **34**−**36** with peptide-derived phosphonates **47** and **48**[1c] afforded peptides **49**−**51** in 83−86% yield. The products were obtained as the *Z* isomers, as shown in the nuclear Overhauser enhancement spectroscopy (NOESY) experiments (Supporting information). Interestingly, with ketone substrate **36**, the reaction took place chemoselectively, and only the aldehyde reacted with the phosphonate. In all of the cases, no epimerizations were observed under the mild reaction conditions, and the desired products were obtained with high enantiomeric (or diastereomeric) purity.

Since the amino group from **34** to **36** could be used to attach another peptide chain, this methodology could allow the creation of new branched peptides, where turns or other secondary structure elements could be induced.[18] The introduction of amino acids containing aryl ketones in these peptides could be particularly interesting since they not only are components of bioactive compounds such as daptomycin (Cubicin),[19] but some, such as 6-(2-dimethylaminonaphthoyl) alanine (DANA)/aladan,[20a,b] or AcF,[20c] serve as fluorophores in medical probes and molecular imaging.[20]

This versatile methodology, which allows the creation of three new chains with stereochemical control will be used to create libraries of potential antimicrobial compounds against pathogens and phytopathogens.[21] These results will be communicated in due course.

CONCLUSIONS

A novel, Hyp-derived "doubly customizable unit" for the ready generation of libraries of amines and amino acid-derived compounds, including modified peptides, is presented herein. This unit can be cleaved at two points, followed by the introduction of new functionalities. Starting from readily available, low-cost 4*R*-hydroxy-L-proline, three new chains are generated and can be manipulated independently to afford a diversity of products with tailored substituents.

Moreover, the process takes place with stereochemical control, and either pure *R* or *S* isomers can be obtained with small variations of the synthetic route. In two transformation cycles, the customizable Hyp unit is converted into *β*-amino aldehydes, diamines, *β*-amino acid derivatives, including N-alkylated ones, or modified peptides. Many of these products are high-profit compounds but, in spite of their commercial value, are still scarce.

The first step is a one-pot radical decarboxylation−oxidation−alkylation reaction, where the carboxyl group at C-2 is removed and replaced by an alkyl chain. The stereochemistry of the new product is controlled by the adjacent stereogenic center at C-4. In a second transformation cycle, the reactive hydroxy group at C-4 is deprotected and activated for a second scission, which cleaves the C_4-C_5 bond. The resulting product has a new acyclic *α*-chain and an *N,O*-acetal that can be processed separately, increasing the library diversity.

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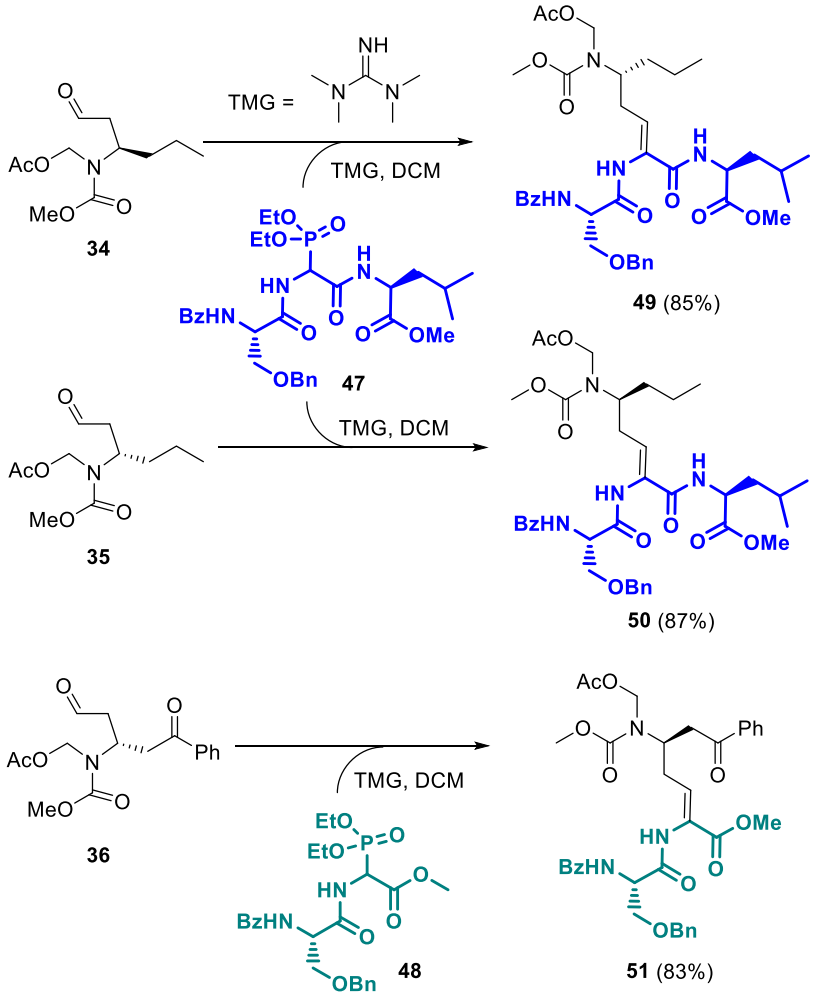
Scheme 9. Preparation of Modified Peptides



The synthesis of branched and modified peptides, including some with rigid dehydroamino acid units, is illustrated as well. The process takes place under mild conditions and good overall yields. The versatility of this doubly customizable unit allows the synthesis of many different structures and will be further explored in the future.

EXPERIMENTAL SECTION

General Methods. Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. Melting points were determined by a hot-stage apparatus and were uncorrected. Optical rotations were measured at the sodium line and ambient temperature (26 °C) in $CHCl_3$ solutions. NMR spectra were determined at 500 or 400 MHz for ^1H and 125.7 or 100.6 MHz for ^{13}C, at 26 or 70 °C, as stated for each case. Sometimes, due to slower rotamer interconversion at 26 °C, two (or more) sets of signals were visible at room temperature, while only one set of signals (rotamer average) was seen at 70 °C due to faster rotamer interconversion. For some compounds, the ^1H NMR spectra show some signals as broad bands (br b) due to equilibria between rotamers.

^1H NMR spectra are reported as follows (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, q = quartet, m = multiplet, br = broad, br b = broad band, br s = broad singlet; coupling constant(s) in Hertz). Mass spectra were recorded using electrospray ionization techniques (ESI) or electronic impact (EI); the latter was determined at 70 eV using an ion trap mass analyzer. Merck silica gel 60 PF_{254} and 60 (0.063−0.2 mm) were used for preparative thin-layer chromatography (TLC) and column chromatography, respectively. The reagent for TLC analysis was $KMnO_4$ in $NaOH/K_2CO_3$ aqueous (aq) solution, and the TLC was heated until development of color.

Preparation of Scission Substrates for Transformation Cycle 1. The characterization data of the following compounds was already reported: Compound **7**;[4c] compounds **9**,[5b] **10**, and **12**;[8d] compound **17**;[22] product **22**;[10] and compounds **23** and **24**.[8c]

*(2S,4R)-4-(Benzyloxy)-N-(methoxycarbonyl)-L-proline (**8**).* 4*R*-Benzyloxy-*N*-(methoxycarbonyl) proline methyl ester **52**[23] (204 mg, 0.70 mmol) was dissolved in 1 M KOH in 9:1 methanol (MeOH)/H_2O (5 mL), and the reaction mixture was stirred at 0 °C for 3 h. Then, 5% aq HCl was added until pH 2 and the mixture was extracted by ethyl acetate (EtOAc). The organic layer was dried over sodium sulfate, filtered, and the solvent was removed under vacuum, affording compound **8** as a viscous oil (194 mg, 99%): $[\alpha]_D^{20}$ −57 (*c* 0.15, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1699, 1455, 1394, 1199 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.30−7.25 (m, 4H), 7.25−7.20 (m, 1H), 4.52−4.48 (m, 2H), 4.43 (t, J = 7.4 Hz, 1H), 4.24−4.19 (m, 1H), 3.67 (s, 3H), 3.68−3.62 (m, 1H), 3.58 (dd, J = 11.5, 5.0 Hz, 1H), 2.44−2.35 (m, 1H), 2.19 (ddd, J = 13.3, 6.4, 5.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$, 125.7 MHz, 26 °C): δ 173.9/173.6 (C), 155.9/155.4 (C), 138.6 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 77.3/76.4 (CH), 71.2 (CH), 58.3/57.9 (CH_3), 52.5 (CH_3), 52.4/52.1 (CH_2), 37.0/35.8 (CH_2). High-resolution mass spectrometry (HRMS) (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{17}NO_5Na$

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302.1004; found 302.1004. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.38; H, 6.27; N, 5.26.

*Methyl (1S,4S)-3-Oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (**16**).* A solution of (2*S*,4*R*)-*N*-methoxycarbonyl-4-hydroxy-L-proline **15** (800 mg, 4.23 mmol) and triphenylphosphine (1.27 g, 4.84 mmol) in dry tetrahydrofuran (THF) (80 mL) was cooled to 0 °C and treated with diethylazodicarboxylate (0.76 mL, 4.84 mmol). The mixture was stirred at room temperature for 20 h; then, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone, 97:3), yielding compound **16** as a viscous oil (512 mg, 71%): $[\alpha]_D^{20}$ +53 (*c* 0.31, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1801, 1709, 1450, 1392, 1329, 1121 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 26 °C): δ 5.10−5.09 (m, 1H), 4.65−4.55 (m, 1H), 3.74 (s, 3H), 3.58 (d, *J* = 10.5 Hz, 1H), 3.48 (d, *J* = 10.5 Hz, 1H), 2.25−2.21 (m, 1H), 2.02 (d, *J* = 11 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 170.7 (C), 155.0 (C), 78.3 (CH), 57.4 (CH), 53.1 (CH_3), 50.0 (CH_2), 39.1 (CH_2). MS *m*/*z* (rel intensity) 171 (M^+, 3), 127 ($M^+ - CO_2$, 16). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_7H_9NO_4$ 171.0532; found 171.0536; $[M - CO_2]^+$ calcd for $C_6H_9NO_2$ 127.0633; found 127.0638. Anal. calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.17; H, 5.52; N, 8.01.

*Methyl (2S,4S)-4-(Hydroxy)-N-(methoxycarbonyl)proline (**17**).* Compound **16** (220 mg, 1.29 mmol) was dissolved in MeOH (10 mL) and treated at 0 °C with sodium methoxide (348 mg, 6.45 mmol). The reaction mixture was stirred for 6 h and then was poured into water and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 30:70), yielding compound **17** as a viscous oil (215 mg, 83%): $[\alpha]_D^{20}$ −22 (*c* 0.65, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3606, 3476, 1728, 1702, 1456, 1391, 1084 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 4.42−4.36 (m, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.65−3.55 (m, 2H), 2.87 (br s, 1H, OH), 2.32 (ddd, *J* = 14.0, 9.5, 4.5 Hz, 1H), 2.11 (d, *J* = 13.9 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 174.7 (C), 155.2 (C), 70.5 (CH), 58.1 (CH), 55.9 (CH_2), 52.6 (CH_3), 52.5 (CH_3), 38.2 (CH_2). MS *m*/*z* (rel intensity) 203 (M^+, 1), 144 ($M^+ - CO_2Me$, 100). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_8H_{13}NO_5$ 203.0794; found 203.0799; $[M - CO_2Me]^+$ calcd for $C_6H_{10}NO_3$ 144.0661; found 144.0667. Anal. calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.10; H, 6.68; N, 6.87.

*Methyl (2S,4S)-4-(Benzyloxy)-N-(methoxycarbonyl)proline (**18a**).* A solution of the hydroxyproline derivative **17** (300 mg, 1.48 mmol) in dry dimethylformamide (DMF) (5 mL) was treated with benzyl bromide (0.26 mL, 2.2 mmol) and silver oxide (342 mg, 1.48 mmol). The reaction mixture was stirred at room temperature, in the absence of light, for 16 h. Then, it was filtered and washed with 5% aq HCl and water, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc 80:20), yielding compound **18a** as a viscous oil (296 mg, 68%): $[\alpha]_D^{20}$ −33 (*c* 0.62, MeOH). IR ($CHCl_3$) ν_{max}: 1746, 1699, 1455, 1228, 1096 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.33−7.23 (m, 5H), 4.45 (s, 2H), 4.43−4.37 (m, 1H), 4.14−4.08 (m, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.70−3.50 (m, 2H), 2.40−2.32 (m, 1H), 2.32−2.25 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 172.2 (C), 155.3 (C), 137.9 (C), 128.4 (2 × CH), 127.7 (CH), 127.5 (2 × CH), 76.1 (CH), 71.0 (CH_2), 57.9 (CH), 52.5 (CH_3), 52.1 (CH_3), 52.0 (CH_2), 36.4/35.3 (CH_2). MS *m*/*z* (rel intensity) 293 (M^+, <1), 91 ($PhCH_2$, 100). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{19}NO_5$ 293.1263; found 293.1261; $[PhCH_2]^+$ calcd for C_7H_7 91.0548; found 91.0550. Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.22; H, 6.69; N, 4.44.

*(2S,4S)-4-(Benzyloxy)-N-(methoxycarbonyl)proline (**18**).* Methyl ester **18a** (200 mg, 0.68 mmol) was dissolved in 1 M KOH in 9:1 MeOH/H_2O (5 mL), and the solution was stirred at 0 °C for 3 h. Then, 5% aq HCl was added until pH 2, and the mixture was extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, affording compound **18** as a viscous oil (170 mg, 90%): $[\alpha]_D^{20}$ −24 (*c* 0.24, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1755, 1737, 1701, 1455, 1393, 1094 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.34−7.22 (m, 5H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.40−4.32 (m, 1H), 4.20−4.16 (m, 1H), 3.68 (s, 3H), 3.67−3.63 (m, 1H), 3.52 (dd, *J* = 11.5, 2.5 Hz, 1H), 2.45−2.33 (m, 2H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 70 °C): δ 175.2 (C), 161.0 (C), 139.5 (C), 129.3 (2 × CH), 128.6 (2 × CH), 128.0 (CH), 72.0 (CH), 65.3 (CH_2), 59.1 (CH), 53.2 (CH_2), 53.1 (CH_3), 36.6 (CH_2). MS *m*/*z* (rel intensity) 279 (M^+, 1), 91 ($PhCH_2$, 100). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{17}NO_5$ 279.1107; found 279.1111; $[PhCH_2]^+$ calcd for C_7H_7 91.0548; found 91.0545. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.48; H, 6.38; N, 4.86.

*Methyl (2S,4S)-4-(tert-Butyldiphenylsilyloxy)-N-(methoxycarbonyl)proline (**19a**).* Compound **17** (1.0 g, 4.92 mmol) was dissolved in dry DMF (15 mL) and treated with imidazole (1.26 g, 18.51 mmol) and *tert*-butyldiphenylsilyl chloride (3.40 g, 12.38 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, poured into water, and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc 80:20), yielding compound **19a** as a viscous oil (1.45 mg, 67%): $[\alpha]_D^{20}$ −29 (*c* 0.43, MeOH). IR ($CHCl_3$) ν_{max}: 1754, 1696, 1455, 1394, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ_H 7.68−7.61 (m, 4H), 7.47−7.36 (m, 6H), 4.39−4.35 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.60−3.40 (m, 2H), 2.28−2.12 (m, 2H), 1.04 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz, 26 °C): δ 172.3/172.1 (C), 155.5/155.1 (C), 135.68 (2 × CH), 135.65 (2 × CH), 133.33/133.25 (C), 133.13/133.11 (C), 129.90/129.88 (CH), 129.86/129.84 (CH), 127.78/127.76 (2 × CH), 127.74/127.72 (2 × CH), 71.6/70.7 (CH), 57.9/57.7 (CH), 55.0/54.5 (CH_2), 55.59/52.55 (CH_3), 52.2 (CH_3), 39.4/38.4 (CH_2), 26.7 (3 × CH_3), 18.9 (C). MS *m*/*z* (rel intensity) 441 (M^+, <1), 384 ($M^+ - {}^tBu$, 100). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{24}H_{31}NO_5Si$ 441.1972; found 441.1988; $[M - {}^tBu]^+$ calcd for $C_{20}H_{22}NO_5Si$ 384.1267; found 384.1267. Anal. calcd for $C_{24}H_{31}NO_5Si$: C, 65.28; H, 7.08; N, 3.17. Found: C, 65.46; H, 7.35; N, 3.00.

*(2S,4S)-4-(tert-Butyldiphenylsilyloxy)-N-(methoxycarbonyl)-proline (**19**).* The methyl ester **19a** (860 mg, 1.95 mmol) was dissolved in 1 M KOH in 9:1 MeOH/H_2O (8 mL), and the reaction mixture was stirred at 0 °C for 16 h. Then, 5% aq HCl was added until pH 2 and the mixture was extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, affording compound **19** as a viscous oil (781 mg, 94%): $[\alpha]_D^{20}$ −33 (*c* 0.44, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1754, 1701, 1457, 1393, 1093 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.74−7.60 (m, 4H), 7.48−7.32 (m, 6H), 4.43−4.32 (m, 2H), 3.67 (s, 3H), 3.48−3.39 (m, 2H), 2.30−2.20 (m, 2H), 1.04 (s, 6H), 1.03 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 100.6 MHz, 26 °C): δ 175.2/175.0 (C), 157.4/157.3 (C), 137.3 (C), 136.9/136.8 (2 × CH), 136.6 (C), 136.0 (CH), 131.1 (CH), 131.0/130.4 (2 × CH), 128.9/128.5 (4 × CH), 73.3/72.4 (CH), 59.3/59.0 (CH), 56.4/56.0 (CH_2), 53.2 (CH_3), 40.3/39.4 (CH_2), 27.2 (2 × CH_3), 27.1 (CH_3), 19.8 (C). MS *m*/*z* (rel intensity) 426 ($M^+ - H$, <1), 199 ($[Ph_2SiOH]^+$, 100). HRMS (EI) *m*/*z*: $[M - H]^+$ calcd for $C_{23}H_{28}NO_5Si$ 426.1737; found 426.1755; $[Ph_2SiOH]^+$ calcd for $C_{12}H_{11}OSi$ 199.0579; found 199.0579. Anal. calcd for $C_{23}H_{29}NO_5Si$: C, 64.61; H, 6.84; N, 3.28. Found: C, 64.82; H, 6.87; N, 3.11.

General Procedure for the Decarboxylation−Oxidation−Alkylation Process. To a solution of the hydroxyproline substrate (0.2 mmol) in dry dichloromethane (DCM, 4 mL) were added iodine (25 mg, 0.1 mmol) and DIB (129 mg, 0.4 mmol). The resulting mixture was stirred for 3 h at 26 °C, under irradiation with visible light (80 W tungsten-filament lamp). Then, the reaction mixture was cooled to 0 °C and treated with $BF_3{\cdot}OEt_2$ (50 μL, 57 mg, 0.4 mmol) and the nucleophile (0.6 mmol). The mixture was stirred for 1 h and then poured into a 1:1 mixture of 10% aqueous $Na_2S_2O_3$ and

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saturated aqueous $NaHCO_3$ (10 mL), followed by extraction with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to give the 2-alkyl pyrrolidines.

*(2S,4R)-2-Allyl-4-benzyloxy-1-methoxycarbonyl Pyrrolidine (**10**).* Obtained from acid **8** (56 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using allyltrimethylsilane (95 μL, 69 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding product **10** (40 mg, 73%, R_f = 0.11) as a viscous oil: $[\alpha]_D^{20}$ +21 (*c* 0.85, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1686, 1455, 1391, 1121, 1095 cm^{-1}.^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.32−7.22 (m, 5H), 5.81−5.73 (m, 1H), 5.07 (br d, *J* = 8.0 Hz, 1H), 5.05 (br d, *J* = 17.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.09−4.06 (m, 1H), 3.94−3.87 (m, 1H), 3.73−3.68 (m, 1H), 3.68 (s, 3H), 3.43 (dd, *J* = 12.0, 3.5 Hz, 1H), 2.70−2.62 (m, 1H), 2.38 (ddd, *J* = 13.5, 9.0, 8.0 Hz, 1H), 2.06 (ddd, *J* = 13.5, 8.0, 6.0 Hz, 1H), 2.00 (ddd, *J* = 13.5, 4.0, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.5 (C), 138.3 (C), 135.2 (CH), 128.4 (2 × CH), 127.6 (CH), 127.5 (2 × CH), 117.0 (CH_2), 77.2 (CH), 71.3 (CH_2), 56.6 (CH), 52.2 (CH_2), 52.0 (CH_3), 38.9 (CH_2), 35.2 (CH_2). MS *m*/*z* (rel intensity) 274 (M^+ − H, <1), 234 (M^+ − CH_2CHCH_2, 90), 91 ($[PhCH_2]^+$, 100). HRMS (EI) *m*/*z*: $[M - H]^+$ calcd for $C_{16}H_{20}NO_3$ 274.1443; found 274.1445; $[M - CH_2CHCH_2]^+$ calcd for $C_{13}H_{16}NO_3$ 234.1130; found 234.1122; $[PhCH_2]^+$ calcd for C_7H_7 91.0548; found 91.0547. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.69; H, 7.82; N, 5.31.

*(2S,4R)-2-Allyl-4-(tert-butyldiphenylsilyloxy)-1-methoxycarbonyl Pyrrolidine (**11**).* Obtained from the acid **9** (85.4 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using allyltrimethylsilane (95 μL, 69 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 98:2), yielding product **11** (65 mg, 77%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ +17 (*c* 0.90, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1687, 1455, 1391, 1235, 1112 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.69−7.63 (m, 4H), 7.47−7.36 (m, 6H), 5.83−5.76 (m, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 4.38−4.34 (m, 1H), 3.88−3.83 (m, 1H), 3.68 (s, 3H), 3.59−3.53 (m, 1H), 3.33 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.72 (br b, 1H), 2.54 (ddd, *J* = 13.8, 8.8, 8.0 Hz, 1H), 1.98 (ddd, *J* = 13.8, 8.2, 6.0 Hz, 1H), 1.88 (dt, *J* = 13.0, 4.0 Hz, 1H), 1.10 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.5 (C), 135.79 (2 × CH), 135.75 (2 × CH), 135.2 (CH), 133.91 (C), 133.86 (C), 129.85 (CH), 129.83 (CH), 127.78 (2 × CH), 127.76 (2 × CH), 117.0 (CH_2), 71.9 (CH), 56.8 (CH), 54.8 (CH_2), 52.0 (CH_3), 38.9 (CH_2), 38.5 (CH_2), 27.0 (3 × CH_3), 19.1 (C). MS *m*/*z* (rel intensity) 424 (M^+ + H, 6), 366 (M^+ − CMe_3, 100). HRMS (EI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{34}NO_3Si$ 424.2308; found 424.2314; $[M - CMe_3]^+$ calcd for $C_{21}H_{24}NO_3Si$ 366.1525; found 366.1527. Anal. calcd for $C_{25}H_{33}NO_3Si$: C, 70.88; H, 7.85; N, 3.31. Found: C, 70.97; H, 7.85; N, 3.30.

*(2R,4R)-4-Benzyloxy-1-methoxycarbonyl-2-(2-oxo-2-phenylethyl)pyrrolidine (**12**).* Obtained from acid **8** (56 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using 1-phenyl-1-trimethylsiloxyethylene (125 μL, 115 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding product **12** (59.3 mg, 84%, R_f = 0.11) as a viscous oil: $[\alpha]_D^{20}$ +14 (*c* 0.23, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3090, 3066, 1684, 1455, 1391, 1199 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.93 (br d, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.46−7.30 (m, 2H), 7.28−7.22 (m, 5H), 4.48 (s, 2H), 4.47−4.43 (m, 1H), 4.14−4.10 (m, 1H), 3.71−3.64 (m, 1H), 3.67 (s, 3H), 3.62−3.59 (m, 2H), 3.42−3.31 (m, 1H), 2.19 (ddd, *J* = 13.8, 8.2, 5.3 Hz, 1H), 2.10 (br d, *J* = 14.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 199.0 (C), 155.3 (C), 138.1 (C), 137.5 (C), 132.8 (CH), 128.5 (3 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.5 (2 × CH), 77.6 (CH), 71.1 (CH_2), 54.1 (CH), 52.4 (CH_2), 52.1 (CH_3), 43.5 (CH_2), 36.1 (CH_2). MS *m*/*z* (rel intensity) 353 (M^+, 1), 91 ($[PhCH_2]^+$, 100). HRMS (EI) *m*/*z*: $[M]^+$ calcd for $C_{21}H_{23}NO_4$ 353.1627; found 353.1624; $[PhCH_2]^+$ calcd for C_7H_7 91.0548; found 91.0546. Anal. calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.66; H, 6.44; N, 4.02.

*(2R,4R)-4-(tert-Butyldiphenylsilyloxy)-1-methoxycarbonyl-2-(2-oxo-2-phenylethyl)pyrrolidine (**13**) and its (2S,4R)-Isomer (**14**).* Obtained from acid **9** (85.4 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using 1-phenyl-1-trimethylsiloxyethylene (125 μL, 115 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (toluene/EtOAc, 99:1), yielding product **13** (62 mg, 62%, R_f = 0.17) and the minor isomer **14** (25 mg, 25%, R_f = 0.10).

*(2R,4R)-4-(tert-Butyldiphenylsilyloxy)-1-methoxycarbonyl-2-(2-oxo-2-phenylethyl)pyrrolidine (**13**).* $[\alpha]_D^{20}$ +17 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1684, 1455, 1391, 1104, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.64−7.60 (m, 4H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.45−7.31 (m, 8H), 4.48−4.40 (m, 2H), 3.80 (br b, 1H), 3.67 (s, 3H), 3.60−3.40 (m, 3H), 2.16 (ddd, *J* = 13.5, 8.3, 5.0 Hz, 1H), 1.96 (br d, *J* = 14.0 Hz, 1H), 1.06 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 198.9 (C), 155.4 (C), 137.5 (C), 135.7 (4 × CH), 133.7 (C), 133.6 (C), 132.9 (CH), 129.90 (CH), 129.87 (CH), 128.6 (2 × CH), 128.2 (2 × CH), 127.83 (2 × CH), 127.79 (2 × CH), 72.3 (CH), 55.2 (CH_2), 54.2 (CH), 52.1 (CH_3), 43.5 (CH_2), 39.5 (CH_2), 27.0 (3 × CH_3), 19.1 (C). MS *m*/*z* (rel intensity) 444 (M^+ − CMe_3, 47), 199 (Ph_2SiOH, 100), 105 (PhCO, 64). HRMS (EI) *m*/*z*: $[M - CMe_3]^+$ calcd for $C_{26}H_{26}NO_4Si$ 444.1631; found 444.1621; $[Ph_2SiOH]^+$ calcd for $C_{12}H_{11}OSi$ 199.0579; found 199.0586; $[PhCO]^+$ calcd for C_7H_5O 105.0340; found 105.0338. Anal. calcd for $C_{30}H_{35}NO_4Si$: C, 71.82; H, 7.03; N, 2.79. Found: C, 71.58; H, 7.20; N, 2.35.

*(2S,4R)-4-(tert-Butyldiphenylsilyloxy)-1-methoxycarbonyl-2-(2-oxo-2-phenylethyl)pyrrolidine (**14**).* $[\alpha]_D^{20}$ −17 (*c* 0.45, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1686, 1453, 1392, 1113, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.55−7.52 (m, 4H), 7.43 (dd, *J* = 7.2, 7.0 Hz, 1H), 7.35−7.23 (m, 8H), 4.45−4.41 (m, 1H), 4.31 (dddd, *J* = 4.5, 4.5, 4.0, 4.0 Hz, 1H), 3.58 (s, 3H), 3.62−3.52 (m, 1H), 3.43 (br d, *J* = 10.5 Hz, 1H), 3.23 (dd, *J* = 11.3, 4.7 Hz, 1H), 2.74 (dd, *J* = 9.3, 15.3 Hz, 1H), 2.20−2.16 (m, 1H), 1.70 (ddd, *J* = 13.5, 7.0, 6.0 Hz, 1H), 0.96 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 198.4 (C), 155.9 (C), 137.5 (C), 135.7 (4 × CH), 134.0 (C), 133.9 (C), 132.9 (CH), 129.8 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 127.8 (4 × CH), 71.3 (CH), 54.8 (CH_2), 53.8 (CH), 52.1 (CH_3), 43.5 (CH_2), 40.8 (CH_2), 27.0 (3 × CH_3), 19.1 (C). MS *m*/*z* (rel intensity) 444 (M^+ − CMe_3, 65), 105 (PhCO, 100). HRMS (EI) *m*/*z*: $[M - CMe_3]^+$ calcd for $C_{26}H_{26}NO_4Si$ 444.1631; found 444.1631; $[PhCO]^+$ calcd for C_7H_5O 105.0340; found 105.0338. Anal. calcd for $C_{30}H_{35}NO_4Si$: C, 71.82; H, 7.03; N, 2.79. Found: C, 71.74; H, 7.20; N, 3.20.

*(2R,4S)-2-Allyl-4-benzyloxy-1-(methoxycarbonyl)pyrrolidine (**20**).* Obtained from acid **18** (56 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using allyltrimethylsilane (95 μL, 69 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding product **20** (35 mg, 63%, R_f = 0.18) as a viscous oil: $[\alpha]_D^{20}$ −19 (*c* 0.63, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1686, 1455, 1392, 1122, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.32−7.22 (m, 5H), 5.81−5.75 (m, 1H), 5.07−5.02 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.10−4.06 (m, 1H), 3.93−3.88 (m, 1H), 3.73−3.68 (m, 1H), 3.68 (s, 3H), 3.43 (dd, *J* = 11.8, 3.3 Hz, 1H), 2.70−2.60 (m, 1H), 2.38 (ddd, *J* = 13.6, 9.2, 7.9 Hz, 1H), 2.06 (ddd, *J* = 13.6, 8.2, 6.0 Hz, 1H), 2.00 (dt, *J* = 13.6, 3.8 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz, 26 °C): δ 155.5 (C), 138.3 (C), 135.2 (CH), 128.4 (2 × CH), 127.6 (CH),

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127.5 (2 × CH), 117.0 (CH_2), 77.2 (CH), 71.3 (CH_2), 56.6 (CH), 52.2 (CH_2), 52.0 (CH_3), 38.9 (CH_2), 35.2 (CH_2). MS m/z (rel intensity) 275 (M^+, <1), 274 ($M^+ - H$, 1), 91 ($[PhCH_2]^+$, 100). HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{21}NO_3$ 275.1521; found 275.1512; $[M - H]^+$ calcd for $C_{16}H_{20}NO_3$ 274.1443; found 274.1446; $[PhCH_2]^+$ calcd for C_7H_7 91.0548; found 91.0549. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.51; H, 8.06; N, 5.00.

*(2R,4S)-2-Allyl-4-(tert-butyldiphenylsilyloxy)-1-methoxycarbonyl Pyrrolidine (**21**).* Obtained from acid **19** (85.4 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using allyltrimethylsilane (95 μL, 69 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 98:2), yielding product **21** (60 mg, 71%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ −20 (*c* 0.47, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1685, 1455, 1391, 1236, 1112 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ_H 7.65−7.61 (m, 4H), 7.42−7.34 (m, 6H), 5.81−5.74 (m, 1H), 5.08 (d, J = 17.0 Hz, 1H), 5.05 (d, J = 10.0 Hz, 1H), 4.35−4.31 (m, 1H), 3.86−3.80 (m, 1H), 3.65 (s, 3H), 3.59−3.45 (m, 1H), 3.31 (dd, J = 11.3, 3.2 Hz, 1H), 2.77−2.63 (m, 1H), 2.51 (1H, ddd, J = 13.5, 9.0, 8.0 Hz, 1H), 1.94 (ddd, J = 14.0, 8.0, 6.0 Hz, 1H), 1.85 (ddd, J = 13.0, 4.0, 3.5 Hz, 1H), 1.07 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.5 (C), 135.7 (4 × CH), 135.2 (CH), 133.8 (2 × C), 129.8 (2 × CH), 127.7 (4 × CH), 117.1 (CH_2), 71.9 (CH), 56.8 (CH), 54.8 (CH_2), 52.0 (CH_3), 38.8 (CH_2), 38.4 (CH_2), 27.0 (3 × CH_3), 19.1 (C). MS m/z (rel intensity) 422 ($M^+ - H$, 6). HRMS (EI) m/z: $[M - H]^+$ calcd for $C_{25}H_{32}NO_3Si$ 422.2151; found 422.2158. Anal. calcd for $C_{25}H_{33}NO_3Si$: C, 70.88; H, 7.85; N, 3.31. Found: C, 70.76; H, 7.72; N, 3.70.

*(2S,4R)-2-Allyl-4-(tert-butyldimethylsilyloxy)-1-methoxycarbonyl Pyrrolidine (**23**).* Obtained from acid **22** (61 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using allyltrimethylsilane (95 μL, 69 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 95:5), yielding product **23** (46 mg, 77%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ +21 (*c* 0.40, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1685, 1455, 1391, 1257, 1085 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ_H 5.82−5.73 (m, 1H), 5.07 (dq, J = 17.0, 1.5 Hz, 1H), 5.05 (dq, J = 10.0, 1.0 Hz, 1H), 4.35−4.31 (m, 1H), 3.91−3.87 (m, 1H), 3.70 (s, 3H), 3.70−3.65 (m, 1H), 3.23 (dd, J = 11.3, 3.8 Hz, 1H), 2.67 (br s, 1H), 2.42 (ddd, J = 14.0, 9.0, 8.5 Hz, 1H), 2.06 (ddd, J = 13.8, 8.5, 6.0 Hz, 1H), 1.79 (dt, J = 13.2, 4.0 Hz, 1H), 0.91 (s, 9H), 0.076 (s, 3H), 0.074 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.5 (C), 135.3 (CH), 116.9 (CH_2), 70.9 (CH), 56.8 (CH), 55.1 (CH_2), 52.0 (CH_3), 38.7 (2 × CH_2), 25.8 (3 × CH_3), 18.0 (C), −4.86 (CH_3), −4.89 (CH_3). MS m/z (rel intensity) 258 ($M^+ - CH_2CH{=}CH_2$, 100). HRMS (EI) m/z: $[M - CH_2CH{=}CH_2]^+$ calcd for $C_{12}H_{24}NO_3Si$ 258.1525; found 258.1513. Anal. calcd for $C_{15}H_{29}NO_3Si$: C, 60.16; H, 9.76; N, 4.68. Found: C, 60.33; H, 9.74; N, 4.62.

*(2R,4R)-4-(tert-Butyldimethylsilyloxy)-1-methoxycarbonyl-2-(2-oxo-2-phenylethyl)pyrrolidine (**24**).* Obtained from acid **22** (61 mg, 0.2 mmol) according to the general scission−oxidation−alkylation sequence using 1-phenyl-1-trimethylsiloxyethylene (125 μL, 115 mg, 0.6 mmol) as the nucleophile. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 90:10), yielding product **24** (50 mg, 66%, R_f = 0.11) as a viscous oil: $[\alpha]_D^{20}$ +19 (*c* 0.65, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1683, 1455, 1391, 1257, 1103 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.97 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.43 (dd, J = 8.0, 7.5 Hz, 2H), 4.47−4.37 (m, 2H), 3.68 (s, 3H), 3.67−3.63 (m, 2H), 3.42−3.35 (m, 2H), 2.24 (ddd, J = 13.5, 8.5, 5.0 Hz, 1H), 1.88 (br d, J = 13.5 Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 199.0 (C), 155.4 (C), 137.6 (C), 132.8 (CH), 128.5 (2 × CH), 128.1 (2 × CH), 71.3 (CH), 55.4 (CH_2), 54.2 (CH), 52.1 (CH_3), 43.8 (CH_2), 40.0 (CH_2), 25.8 (3 × CH_3), 18.0 (C), −4.9 (CH_3), −5.0 (CH_3). MS m/z (rel intensity) 320 ($M^+ - CMe_3$, 67), 105 (PhCO, 100). HRMS (EI) m/z: $[M - CMe_3]^+$ calcd for $C_{16}H_{22}NO_4Si$ 320.1318; found 320.1310; $[PhCO]^+$ calcd for C_7H_5O 105.0340; found 105.0338. Anal. calcd for $C_{20}H_{31}NO_4Si$: C, 63.62; H, 8.28; N, 3.71. Found: C, 63.64; H, 8.39; N, 3.87.

*(2R,4R)-2-(1,1-Dimethyl-2-methoxy-2-oxoethyl)-4-(tert-butyldimethylsilyloxy)-1-(methoxycarbonyl)pyrrolidine (**25**) and Its (2S,4R)-Isomer (**26**).* Obtained from acid **22** (61 mg, 0.2 mmol) using 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (125 μL, 108 mg, 0.6 mmol) according to the general decarboxylation−oxidation−alkylation sequence. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding products **25** (27 mg, 38%, R_f = 0.12) and **26** (25 mg, 35%, R_f = 0.15) as viscous oils.

*Product **25**.* $[\alpha]_D^{20}$ +11 (*c* 0.41, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1726, 1697, 1450, 1388, 1134 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 4.30 (dd, J = 8.7, 7.1 Hz, 1H), 4.29−4.23 (m, 1H), 3.96 (dd, J = 11.3, 7.3 Hz, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 2.89 (dd, J = 11.2, 8.0 Hz, 1H), 2.37−2.31 (m, 1H), 1.66−1.60 (m, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 0.89 (s, 9H), 0.073 (s, 3H), 0.067 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 70 °C): δ 178.9 (C), 158.2 (C), 70.8 (CH), 63.4 (CH), 55.8 (CH_2), 53.1 (CH_3), 52.4 (CH_3), 48.3 (C), 37.8 (CH_2), 26.2 (3 × CH_3), 22.7 (CH_3), 21.5 (CH_3), 18.8 (C), −4.7 (CH_3), −4.8 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{33}NO_5SiNa$ 382.2026; found 382.2028. Anal. calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.85; H, 8.93; N, 3.52.

*Product **26**.* $[\alpha]_D^{20}$ −13 (*c* 0.59, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1725, 1698, 1448, 1385, 837 cm^{-1}. ^1H NMR (500 MHz, CD_3OD, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 4.42−4.31 (m, 2H), 3.72 (br dd, J = 12.0, 4.0 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.15 (dd, J = 12.0, 3.5 Hz, 1H), 1.96−1.86 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (CD_3OD, 125.7 MHz, 70 °C): δ 178.8 (C), 159.7 (C), 72.2 (CH), 63.7 (CH), 58.1 (CH_2), 53.0 (CH_3), 52.4 (CH_3), 48.5 (C), 38.4 (CH_2), 26.1 (3 × CH_3), 22.3 (CH_3), 21.7 (CH_3), 18.7 (C), −4.7 (CH_3), −4.8 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{33}NO_5SiNa$ 382.2026; found 382.2026. Anal. calcd for $C_{17}H_{33}NO_5Si$: C, 56.79; H, 9.25; N, 3.90. Found: C, 56.90; H, 8.87; N, 3.59.

General Procedures for the Synthesis of 2-alkyl-4-(hydroxy)pyrrolidines. *Method A (PG = Bn).* Pd/C (10%, 30 mg) was added to a solution of the pyrrolidine derivative (0.3 mmol) in dry MeOH (4 mL). The mixture was purged with successive cycles of vaccuum/hydrogen to remove air and replace it by hydrogen (1 atm, H_2 balloon) and stirred at room temperature for 16. Then, it was filtered over celite, and the filtrate was concentrated under vacuum to afford 4-(hydroxy)pyrrolidines.

Method B (PG = ^{t}BuMe$_2$Si or ^{t}BuPh$_2$Si). The silylated product (0.3 mmol) was dissolved in dry THF (3 mL) and the mixture was cooled to 0 °C and treated with tetra-*n*-butylammonium fluoride (TBAF) (124.5 mg, 0.45 mmol). The solution was stirred at room temperature for 3 h and then poured into water and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, and the residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to give 4-(hydroxy)pyrrolidines.

*(2R,4S)-4-(Hydroxy)-2-(propyl)-N-(methoxycarbonyl)pyrrolidine (**27**).* Obtained from product **20** (82.5 mg, 0.3 mmol) according to procedure A. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 90:10), yielding compound **27** as a viscous oil (50.5 mg, 90%, R_f = 0.13): $[\alpha]_D^{20}$ −42 (*c* 0.27, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3613, 1684, 1455, 1392, 1119 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ_H 4.42−4.38 (m, 1H), 3.88−3.83 (m, 1H), 3.75 (dd, J = 11.8, 6.0 Hz, 1H), 3.69 (s, 3H), 3.27 (ddd, J = 12.0, 4.0, 1.0 Hz, 1H), 2.20 (ddd, J = 13.5, 8.5, 6.3 Hz, 1H), 1.97−1.88 (m, 1H), 1.74 (ddd, J = 13.5, 4.3, 3.8 Hz, 1H), 1.67 (br s, 1H), 1.60−1.53 (m, 1H), 1.41−1.27 (m, 2H), 0.95 (t, J = 7.4

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Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.7 (C), 70.6 (CH), 57.2 (CH), 54.7 (CH_2), 52.1 (CH_3), 39.1 (CH_2), 37.4 (CH_2), 19.5 (CH_2), 13.9 (CH_3). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_9H_{17}NO_3Na$ 210.1106; found 210.1106. Anal. calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.63; H, 9.36; N, 7.58.

*(2R,4S)-2-Allyl-4-hydroxy-1-methoxycarbonylpyrrolidine (**28**).* Obtained from compound **21** (127 mg, 0.3 mmol) according to the general method B. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding product **28** (52 mg, 94%, R_f = 0.25) as a viscous oil: $[\alpha]_D^{20}$ −47 (*c* 0.67, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3611, 1686, 1455, 1391, 1121, 1075 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 5.84−5.74 (m, 1H), 5.12−5.05 (m, 2H), 4.43−4.36 (m, 1H), 3.96−3.90 (m, 1H), 3.72 (dd, *J* = 11.7, 6.5 Hz, 1H), 3.70 (s, 3H), 3.31 (ddd, *J* = 11.5, 3.5, 1.1 Hz, 1H), 2.71−2.64 (m, 1H), 2.44 (br ddd, *J* = 14.0, 9.0, 8.0 Hz, 1H), 2.16 (ddd, *J* = 14.0, 8.0, 5.5 Hz, 1H), 1.83 (ddd, *J* = 13.5, 4.0, 3.5 Hz, 1H), 1.71 (br s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.6 (C), 135.1 (CH), 117.4 (CH_2), 70.5 (CH), 56.8 (CH), 55.1 (CH_2), 52.1 (CH_3), 39.0 (CH_2), 38.4 (CH_2). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_9H_{15}NO_3Na$ 208.0950; found 208.0948. Anal. calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.44; H, 8.12; N, 7.86.

*(2S,4R)-4-(Hydroxy)-2-(propyl)-N-(methoxycarbonyl)pyrrolidine (**29**).* Obtained from compound **10** (82.5 mg, 0.3 mmol) according to the general method A. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding **29** as a viscous oil (45 mg, 80%, R_f = 0.24): $[\alpha]_D^{20}$ +39 (*c* 0.16, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3610, 3448, 1683, 1455, 1392 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 4.43−4.37 (m, 1H), 3.89−3.84 (m, 1H), 3.76 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.69 (s, 3H), 3.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.20 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 1.96−1.89 (m, 1H), 1.74 (dt, *J* = 13.5, 4.0 Hz, 1H), 1.63 (br b, 1H), 1.61−1.54 (m, 1H), 1.41−1.27 (m, 2H), 0.95 (dd, *J* = 7.5, 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.7 (C), 70.7 (CH), 57.3 (CH), 54.7 (CH_2), 52.0 (CH_3), 39.2 (CH_2), 37.4 (CH_2), 19.5 (CH_2), 13.9 (CH_3). MS *m/z* (rel intensity) 187 (M^+, <1), 144 ([M − propyl]$^+$, 100). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_9H_{17}NO_3$ 187.1208; found 187.1212; [M − propyl]$^+$ calcd for $C_6H_{10}NO_3$ 144.0661; found 144.0654. Anal. calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.70; H, 9.21; N, 7.30.

*(2R,4R)-4-(Hydroxy)-2-(2-oxo-2-phenylethyl)-N-(methoxycarbonyl)pyrrolidine (**30**).* Obtained from silyl ether **24** (113 mg, 0.3 mmol) according to the general method B. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding alcohol **30** (69.5 mg, 88%, R_f = 0.23) as a viscous oil. This product was also obtained (67 mg, 85%) from compound **12** (106 mg, 0.3 mmol) according to method A: $[\alpha]_D^{20}$ +12 (*c* 0.58, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3431, 1684, 1455, 1391 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.54 (dd, *J* = 7.0, 6.5 Hz, 1H), 7.44 (dd, *J* = 8.0, 7.5 Hz, 2H), 4.49−4.41 (m, 2H), 3.68 (s, 3H), 3.68−3.65 (m, 2H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.42 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.30 (ddd, *J* = 14.0, 8.5, 5.3 Hz, 1H), 2.08 (br s, 1H), 1.93 (br d, *J* = 13.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 199.3 (C), 155.5 (C), 137.5 (C), 133.0 (CH), 128.6 (2 × CH), 128.2 (2 × CH), 70.7 (CH), 55.3 (CH_2), 54.3 (CH), 52.2 (CH_3), 43.8 (CH_2), 39.6 (CH_2). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{17}NO_4Na$ 286.1055; found 286.1051. Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.78; H, 6.68; N, 5.32.

*(2S,4R)-2-Allyl-4-hydroxy-1-(methoxycarbonyl)pyrrolidine (**31**).* Obtained from silyl ether **23** (90 mg, 0.3 mmol) according to the general method B. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding product **31** (49 mg, 89%, R_f = 0.25) as a viscous oil: $[\alpha]_D^{20}$ +43 (*c* 0.73, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3611, 3441, 1685, 1455, 1392 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 5.82−5.74 (m, 1H), 5.12−5.05 (m, 2H), 4.41−4.37 (m, 1H), 3.95−3.90 (m, 1H), 3.72 (dd, *J* = 11.7, 5.7 Hz, 1H), 3.69 (s, 3H), 3.30 (dd, *J* = 11.8, 3.6 Hz, 1H), 2.70−2.63 (m, 1H), 2.43 (ddd, *J* = 13.8, 8.7, 8.0 Hz, 1H), 2.16 (ddd, *J* = 13.8, 8.3, 6.0 Hz, 1H), 1.87 (br b, 1H), 1.83 (dt, *J* = 13.6, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 155.6 (C), 135.1 (CH), 117.3 (CH_2), 70.5 (CH), 56.8 (CH), 55.1 (CH_2), 52.1 (CH_3), 39.0 (CH_2), 38.5 (CH_2). MS *m/z* (rel intensity) 185 (M^+, <1), 144 ([M − allyl]$^+$, 100). HRMS (EI) *m/z*: $[M]^+$ calcd for $C_9H_{15}NO_3$ 185.1052; found 185.1059; [M − allyl]$^+$ calcd for $C_6H_{10}NO_3$ 144.0661; found 144.0654. Anal. calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.28; H, 8.34; N, 7.52.

*N-Methoxycarbonyl-(2S,4R)-[4-(hydroxy)-2-(1,1-dimethyl-2-methoxy-2-oxoethyl)]pyrrolidine (**32**).* Obtained from the silyl ether **25** (108 mg, 0.3 mmol) according to method B. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 50:50), yielding alcohol **32** (65.5 mg, 89%, R_f = 0.27) as a viscous oil: $[\alpha]_D^{20}$ +29 (*c* 0.63, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3445, 1726, 1697, 1450, 1388 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 26 °C): δ 4.26 (dd, *J* = 8.5, 7.5 Hz, 1H), 4.21 (dddd, *J* = 7.9, 7.9, 7.9, 7.8 Hz, 1H), 4.07−3.97 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 2.91 (dd, *J* = 11.3, 8.2 Hz, 1H), 2.76 (br s, 1H), 2.34 (dt, *J* = 13.5, 8.2 Hz, 1H), 1.63 (ddd, *J* = 13.2, 7.6, 6.6 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 177.4 (C), 156.4 (C), 68.7 (CH), 62.1 (CH), 54.0 (CH_2), 52.5 (CH_3), 51.9 (CH_3), 46.9 (C), 36.0 (CH_2), 22.2 (CH_3), 21.0 (CH_3). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{19}NO_5Na$ 268.1161; found 268.1165. Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.68; H, 8.21; N, 5.82.

*N-Methoxycarbonyl-(2R,4R)-[4-(hydroxy)-2-(1,1-dimethyl-2-methoxy-2-oxoethyl)]pyrrolidine (**33**).* Obtained from silyl ether **26** (108 mg, 0.3 mmol) according to method B. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 50:50), yielding alcohol **33** (68 mg, 93%, R_f = 0.24) as a viscous oil: $[\alpha]_D^{20}$ −26 (*c* 1.10, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3439, 1726, 1697, 1449, 1387 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 26 °C): δ 4.47 (dd, *J* = 8.0, 7.5 Hz, 1H), 4.32−4.30 (m, 1H), 3.85−3.72 (m, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.19 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.02 (br s, 1H), 2.02 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.86 (ddd, *J* = 13.5, 7.5, 5.5 Hz, 1H), 1.11 (s, 3H), 1.08 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 177.1 (C), 157.5 (C), 70.0 (CH), 61.9 (CH), 56.6 (CH_2), 52.6 (CH_3), 51.9 (CH_3), 46.7 (C), 36.6 (CH_2), 21.7 (CH_3), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{19}NO_5Na$ 268.1161; found 268.1162. Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.64; H, 7.95; N, 5.69.

General Procedure for the Scission of the Pyrrolidine C_4−C_5 Bond. To a solution of the 2-alkyl-2-hydroxypyrrolidine (0.2 mmol) in dry dichloromethane (4 mL) were added iodine (25 mg, 0.1 mmol) and DIB (129 mg, 0.4 mmol). The resulting mixture was stirred for 3 h at 26 °C, under irradiation with visible light (80 W tungsten-filament lamp). Then, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to give the scission products.

*N-(Acetoxymethyl)-N-(methoxycarbonyl)-(3R)-aminohexanal (**34**).* Obtained from hydroxypyrrolidine **27** (37.5 mg, 0.2 mmol) according to the general pyrrolidine scission procedure. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding aldehyde **34** (31 mg, 63%, R_f = 0.30) as a viscous oil: $[\alpha]_D^{20}$ −16 (*c* 0.10, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1733, 1695, 1454, 1238, 1103, 1046 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 26 °C): δ 9.69 (s, 1H), 5.37 (br d, *J* = 10.0 Hz, 1H), 5.26 (br d, *J* = 10.5 Hz, 1H), 4.48−4.42 (m, 1H), 3.73 (br s, 3H), 2.83−2.67 (m, 1H), 2.58 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.04 (s, 3H), 1.75−1.55 (br b, 1H), 1.55−1.43 (m, 1H), 1.36−1.25 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz, 26 °C): δ 200.3/199.8 (CH), 170.6 (C), 155.9 (C), 70.2 (CH_2), 53.2 (CH), 52.4/51.6 (CH_3), 48.2/47.7 (CH_2), 35.6/35.1 (CH_2), 21.0 (CH_3),

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19.4 (CH_2), 13.7 (CH_3). HRMS (ESI) m/z: $[M + Na + MeOH]^+$ calcd for $C_{12}H_{23}NO_6Na$ 300.1423; found 300.1421. Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.79; H, 7.93; N, 6.03.

*N-(Acetoxymethyl)-N-(methoxycarbonyl)-(3S)-aminohexanal (**35**).* Obtained from the 2-propyl-4-hydroxypyrrolidine **29** (37 mg, 0.2 mmol) according to the general pyrrolidine scission procedure. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding aldehyde **35** (31 mg, 64%, R_f = 0.30) as a viscous oil: $[\alpha]_D^{20}$ +20 (c 0.66, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3027, 1699, 1450, 1273, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 26 °C): δ 9.69 (1H, s), 5.37 (br d, J = 10.8 Hz, 1H), 5.26 (br d, J = 11.2 Hz, 1H), 4.49–4.42 (m, 1H), 3.73 (br s, 3H), 2.81–2.62 (m, 1H), 2.59 (dd, J = 16.8, 7.0 Hz, 1H), 2.04 (s, 3H), 1.72–1.55 (m, 1H), 1.55–1.40 (m, 1H), 1.25–1.38 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C): δ 200.8 (CH), 172.1 (C), 158.1 (C), 70.9 (CH_2), 55.2 (CH), 53.6 (CH_3), 41.6 (CH_2), 36.7 (CH_2), 20.9 (CH_3), 20.4 (CH_2), 14.1 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{19}NO_5Na$ 268.1161; found 268.1167. Anal. calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.75; H, 7.76; N, 6.00.

*(3R)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-5-(oxo)-5-(phenyl)pentanal (**36**).* Obtained from compound **30** (53 mg, 0.2 mmol) according to the general pyrrolidine scission procedure. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding aldehyde **36** (47 mg, 73%, R_f = 0.24) as a viscous oil: $[\alpha]_D^{20}$ +14 (c 0.33, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1705, 1686, 1449, 1274, 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 9.77 (t, J = 2.0 Hz, 1H), 7.93 (d, J = 7.0 Hz, 2H), 7.56 (dd, J = 7.9, 7.5 Hz, 1H), 7.46 (dd, J = 8.0, 7.5 Hz, 2H), 5.43 (d, J = 13.0 Hz, 1H), 5.41 (d, J = 12.0 Hz, 1H), 4.85–4.76 (m, 1H), 3.73 (s, 3H), 3.63–3.52 (m, 1H), 3.33 (dd, J = 17.5, 6.0 Hz, 1H), 3.09–3.01 (m, 1H), 2.90 (dd, J = 17.2, 5.5 Hz, 1H), 1.97 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 199.3 (C), 197.2 (C), 170.3 (C), 155.7 (C), 137.0 (C), 133.4 (CH), 128.7 (2 × CH), 128.1 (2 × CH), 73.3 (CH_2), 53.0 (CH_3), 50.9 (CH), 47.5 (CH_2), 42.0 (CH_2), 20.7 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}NO_6Na$ 344.1110; found 344.1109. Anal. calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.87; H, 6.27; N, 4.75.

*Methyl (3R)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-2,2-dimethyl-5-oxopentanoate (**37**).* Obtained from compound **32** (49 mg, 0.2 mmol) according to the general pyrrolidine scission procedure. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 80:20), yielding aldehyde **37** (38 mg, 63%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ +15 (c 0.54, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1725, 1572, 1444, 1345, 1015 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 26 °C): δ 9.67 (s, 1H), 5.48–5.32 (br b, 1H), 5.26 (br d, J = 11.5 Hz, 1H), 5.00–4.60 (br b, 1H), 3.75 (br s, 3H), 3.69 (s, 3H), 3.05–2.85 (m, 1H), 2.71 (br d, J = 13.6 Hz, 1H), 2.00 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 199.6 (CH), 176.0 (C), 170.3 (C), 156.7 (C), 70.2 (CH_2), 57.6 (CH), 53.5 (CH_3), 52.2 (CH_3), 46.7 (C), 42.6 (CH_2), 24.4 (CH_3), 22.2 (CH_3), 20.8 (CH_3). HRMS (ESI) m/z: [M + Na + MeOH]$^+$ calcd for $C_{14}H_{25}NO_8Na$ 358.1478; found 358.1468. Anal. calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.59; H, 6.88; N, 4.35.

*Methyl (3S)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-2,2-dimethyl-5-oxopentanoate (**38**).* Obtained from compound **33** (49 mg, 0.2 mmol) according to the general pyrrolidine scission procedure. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 70:30), yielding aldehyde **38** (37 mg, 61%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ −17 (c 0.56, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3022, 1726, 1445 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, 26 °C): δ 9.67 (br s, 1H), 5.48–5.32 (br b, 1H), 5.25 (br d, J = 11.4 Hz, 1H), 5.00–4.60 (m, 1H), 3.76 (br s, 3H), 3.70 (s, 3H), 3.05–2.85 (m, 1H), 2.71 (br d, J = 13.6 Hz, 1H), 2.02 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 199.7 (CH), 176.0 (C), 170.4 (C), 156.7 (C), 70.5 (CH_2), 57.8 (CH), 53.5 (CH_3), 52.2 (CH_3), 46.6 (C), 42.6 (CH_2), 24.4 (CH_3), 22.1 (CH_3), 20.8 (CH_3). HRMS (ESI) m/z: [M + Na + MeOH]$^+$ calcd for $C_{14}H_{25}NO_8Na$ 358.1478; found 358.1466. Anal. calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.26; H, 7.05; N, 4.47.

General Reductive Amination Procedure. A solution of the aldehyde (0.15 mmol) in dry dichloroethane (3 mL) was treated with the corresponding amine (0.17 mmol) and Et_3N (28 μL, 0.2 mmol). The resulting mixture was stirred for 30 min and then $NaBH(OAc)_3$ (95 mg, 0.45 mmol) was added. The stirring continued until the disappearance of the starting material (4–16 h). Then, the mixture was poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate) to give the reductive amination products.

*(3R)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-5-(dibenzylamino)-1-(phenyl)-1-pentanone (**39**).* Obtained from aldehyde **36** (48 mg, 0.15 mmol) according to the general reductive amination procedure using dibenzylamine (33 μL, 34 mg, 0.17 mmol). After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 90:10), yielding diamine **39** (51 mg, 68%) as a viscous oil: $[\alpha]_D^{20}$ +6 (c 0.85, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3091, 3067, 1707, 1449, 1237 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 26 °C) rotamer equilibrium. Two sets of signals at 26 °C: δ 7.87 (d, J = 7.0 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 7.5 Hz, 4H), 7.22 (dd, J = 8.0, 7.0 Hz, 4H), 7.12 (dd, J = 7.6, 7.4 Hz, 2H), 5.35/5.28 (d, J = 10.1 Hz/d, J = 8.0 Hz, 1H), 5.12 (d, J = 11.0 Hz, 1H), 4.65–4.54 (m, 1H), 3.63 (s, 3H), 3.63–3.55 (m, 2H), 3.42–3.37 (m, 2H), 3.40–3.20 (br b, 2H), 2.46–2.40 (m, 2H), 2.05–1.75 (m, 2H), 1.65/1.57 (s/s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C): δ 200.0 (C), 172.0 (C), 158.3/157.4 (C), 140.7 (2 × C), 138.2 (C), 134.4 (CH), 130.2 (2 × CH), 129.7 (4 × CH), 129.3 (4 × CH), 129.2 (2 × CH), 128.1 (2 × CH), 73.1/72.1 (CH_2), 59.3 (2 × CH_2), 53.7/53.5 (CH), 52.7 (CH_3), 50.6 (CH_2), 41.9/41.6 (CH_2), 31.6/30.9 (CH_2), 20.6 (CH_3). HRMS (ESI) m/z: $[M + H - CO_2Me]^+$ calcd for $C_{28}H_{31}N_2O_3$ 443.2335; found 443.2327. Anal. calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.78; H, 7.08; N, 5.92.

*Methyl (3S)-Buten-1-yl(5-(dibenzylamino)-1-oxo-1-phenylpentan-3-yl)carbamate (**40**).* A solution of substrate **39** (45 mg, 0.09 mmol) in dry acetonitrile (2 mL) was treated at 0 °C with allyltrimethylsilane (40 μL, 29 mg, 0.25 mmol) and trimethylsilyl triflate (30 μL, 37 mg, 0.17 mmol). The resulting mixture was stirred for 1.5 h, then poured into satured aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, and the residue was purified by chromatography on silica gel (hexanes/ethyl 80:20) to give compound **40** (31 mg, 71%, R_f = 0.29) as a viscous oil: $[\alpha]_D^{20}$ +2 (c 0.21, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1691, 1573, 1449, 1366, 1003 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 70 °C): δ 7.87 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.46 (dd, J = 8.0, 7.5 Hz, 2H), 7.31 (d, J = 7.6 Hz, 4H), 7.24 (t, J = 7.6 Hz, 4H), 7.16 (dd, J = 7.5, 7.0 Hz, 2H), 5.69–5.61 (m, 1H), 4.94–4.91 (m, 2H), 4.15–4.00 (br b, 3H), 3.61 (d, J = 13.5 Hz, 2H), 3.55 (s, 3H), 3.50 (d, J = 13.5 Hz, 2H), 3.11–2.98 (m, 2H), 2.47 (t, J = 6.8 Hz, 2H), 2.09 (q, J = 7.4 Hz, 2H), 1.95–1.80 (br s, 2H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C): δ 200.5 (C), 158.3 (C), 140.4/140.3 (2 × C), 138.3/138.2 (C), 136.6 (CH), 134.4 (CH), 130.4 (2 × CH), 130.3 (2 × CH), 129.8 (2 × CH), 129.3 (4 × CH), 129.2 (2 × CH), 128.2 (2 × CH), 116.8 (CH_2), 59.4 (2 × CH_2), 54.5 (CH), 53.1 (CH_2), 52.9 (CH_3), 51.0 (CH_2), 47.5/46.1 (CH_2), 35.0/34.3 (CH_2), 31.9/30.9 (CH_2). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{31}H_{36}N_2O_3Na$ 507.2624; found 507.2626. Anal. calcd for $C_{31}H_{36}N_2O_3$: C, 76.83; H, 7.49; N, 5.78. Found: C, 77.05; H, 7.69; N, 5.71.

*Methyl (3R)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-2,2-(dimethyl)-5-dibenzylaminopentanoate (**41**).* Obtained from aldehyde **38** (37 mg, 0.15 mmol) according to the general procedure for the reductive amination (16 h) using dibenzylamine as a reagent (33 μL, 34 mg, 0.17 mmol). After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc,

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40:60), yielding diamine **41** (49 mg, 67%) as a viscous oil: $[\alpha]_D^{20}$ −27 (*c* 1.01, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1716, 1446, 1251, 1131 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz, 26 °C): δ 7.36−7.34 (m, 4H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.21 (dd, *J* = 7.5, 6.5 Hz, 2H), 5.20−5.10 (br b, 2H), 4.67−4.51 (m, 1H), 3.68 (s, 3H), 3.64 (br d, *J* = 13.5 Hz, 2H), 3.54 (s, 3H), 3.33 (br d, *J* = 12.0 Hz, 2H), 2.55−2.45 (m, 1H), 2.34−2.23 (m, 1H), 1.82 (s, 3H), 1.78−1.65 (m, 2H), 1.13 (s, 3H), 1.11 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C): δ 178.2 (C), 171.8 (C), 158.9 (C), 140.7 (2 × C), 130.0 (4 × CH), 129.3 (4 × CH), 128.0 (2 × CH), 70.4 (CH_2), 60.1 (CH), 59.6 (2 × CH_2), 53.9 (CH_3), 52.5 (CH_3), 51.5 (CH_2), 48.6 (C), 26.8 (CH_2), 24.4 (CH_3), 21.7 (CH_3), 20.8 (CH_3). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{37}N_2O_6$ 485.2652; found 485.2644. Anal. calcd for $C_{27}H_{36}N_2O_6$: C, 66.92; H, 7.49; N, 5.78. Found: C, 67.00; H, 7.22; N, 6.03.

*Methyl (R)-5-(Dibenzylamino)-3-[(methoxycarbonyl)(methyl)-amino]-2,2-dimethylpentanoate (**42**).* A solution of substrate **41** (58 mg, 0.12 mmol) in dry acetonitrile (3 mL) was treated at 0 °C with triethylsilane (96 μL, 70 mg, 0.6 mmol) and trimethylsilyl triflate (43 μL, 53 mg, 0.24 mmol). The resulting mixture was stirred for 3 h, then poured into satured aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated under vacuum, and the residue was purified by chromatography on silica gel (hexanes/EtOAc 80:20) to give compound **42** (37 mg, 73%, R_f = 0.20) as a viscous oil: $[\alpha]_D^{20}$ −7 (*c* 0.10, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1730, 1697, 1455, 1232, 1046 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C): δ 7.38 (d, *J* = 7.5 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.26 (t, *J* = 7.0 Hz, 2H), 4.38−4.24 (m, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.62 (br s, 4H), 2.64/2.55 (s/s, 3H), 2.51−2.33 (m, 2H), 1.84−1.67 (m, 2H), 1.20 (br s, 3H), 1.18 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δ 176.9 (C), 157.9 (C), 139.7 (C), 139.6 (C), 128.9 (4 × CH), 128.2 (4 × CH), 126.9 (2 × CH), 60.0 (CH), 59.0 (CH_2), 58.9 (CH_2), 52.5 (CH_3), 51.6 (CH_3), 51.4 (CH_2), 47.4 (C), 30.0 (CH_3), 25.2 (CH_2), 24.1 (CH_3), 22.2 (CH_3). HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{25}H_{34}N_2O_4Na$ 449.2416; found 449.2415. Anal. calcd for $C_{25}H_{34}N_2O_4$: C, 70.40; H, 8.03; N, 6.57. Found: C, 70.31; H, 7.82; N, 6.47.

*Methyl (3S)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-2,2-(dimethyl)-5-morpholinyl-pentanoate (**43**).* Obtained from aldehyde **37** (45 mg, 0.15 mmol) according to the reductive amination procedure using morpholine (15 μL, 15 mg, 0.17 mmol). After usual work-up and solvent removal, the residue was purified by radial chromatography (hexanes/EtOAc, 40:60), yielding diamine **43** (41 mg, 73%, R_f = 0.15) as a viscous oil: $[\alpha]_D^{20}$ +18 (*c* 0.78, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1720, 1570, 1450, 1274, 1138 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 70 °C): δ 5.41 (d, *J* = 10.8 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.60−4.36 (br b, 1H), 3.80−3.67 (m, 4H), 3.67 (s, 6H), 2.46−2.33 (m, 6H), 2.02 (s, 3H), 1.80−1.74 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 70 °C): δ 179.7 (C), 177.7 (C), 157.7 (C), 69.2 (CH_2), 61.9 (CH_2), 61.7 (CH_2), 60.1 (CH), 58.9 (CH_2), 58.7 (CH_2), 58.4 (CH_2), 54.7 (CH_3), 52.8 (CH_3), 48.2 (C), 24.2 (CH_2), 22.6 (2 × CH_3), 20.3 (CH_3). HRMS (ESI) *m*/*z*: $[M - CO_2Me]^+$ calcd for $C_{15}H_{27}N_2O_5$ 315.1920; found 315.1915. Anal. calcd for $C_{17}H_{30}N_2O_7$: C, 54.53; H, 8.08; N, 7.48. Found: C, 54.26; H, 8.44; N, 7.41.

*Methyl (3R)-[N-(Acetoxymethyl)-N-(methoxycarbonyl)amino]-2,2-(dimethyl)-5-morpholinyl-pentanoate (**44**).* Obtained from aldehyde **38** (45 mg, 0.15 mmol) according to the general procedure for the reductive amination, using morpholine (15 μL, 15 mg, 0.17 mmol). After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 40:60), yielding diamine **44** (38 mg, 68%, R_f = 0.15) as a viscous oil: $[\alpha]_D^{20}$ −16 (*c* 1.06, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 1720, 1573, 1450 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 26 °C): δ 5.41 (d, *J* = 11.2 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.63−4.35 (br b, 1H), 3.73 (m, 3H), 3.80−3.50 (m, 4H), 3.66 (s, 3H), 2.55−2.30 (m, 6H), 2.02 (s, 3H), 1.98−1.68 (m, 2H), 1.22 (s, 3H), 1.19 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 70 °C): δ 179.7 (C), 177.7 (C), 157.7 (C), 69.2 (CH_2), 61.9 (CH_2), 61.7 (CH_2), 60.1 (CH), 58.9 (CH_2), 58.5 (CH_2), 58.4 (CH_2), 54.7 (CH_3), 52.8 (CH_3), 48.2 (C), 24.2 (CH_2), 22.6 (2 × CH_3), 20.3 (CH_3). HRMS (ESI) *m*/*z*: $[M - CO_2Me]^+$ calcd for $C_{15}H_{27}N_2O_5$ 315.1920; found 315.1914. Anal. calcd for $C_{17}H_{30}N_2O_7$: C, 54.53; H, 8.08; N, 7.48. Found: C, 54.63; H, 8.04; N, 7.18.

*Methyl (2S,4R)-1-[(R)-3-[(Acetoxymethyl)(methoxycarbonyl)-amino]-5-methoxy-4,4-dimethyl-5-oxopentyl]-4-hydroxypyrrolidine-2-carboxylate (**45**).* Obtained from aldehyde **37** (45.5 mg, 0.15 mmol) according to the reductive amination procedure (16 h) using 4-*trans*-hydroxyproline methyl ester hydrochloride as reagent (31 mg, 0.17 mmol). After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding diamine **45** (33 mg, 51%, R_f = 0.18) as a viscous oil: $[\alpha]_D^{20}$ +40 (*c* 0.21, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3356, 1722, 1568, 1260, 1159 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 26 °C): δ 5.37−5.25 (m, 2H), 4.70−4.38 (br b, 1H), 4.40−4.30 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.47 (t, *J* = 7.6 Hz, 1H), 3.35−3.30 (m, 1H), 2.78−2.68 (m, 1H), 2.46−2.36 (m, 2H), 2.04 (s, 3H), 2.15−1.90 (m, 2H), 1.80−1.69 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C) δ 178.1 (C), 175.4 (C), 171.9 (C), 159.9 (C), 70.6 (CH_2), 70.5 (CH), 65.9 (CH), 62.3 (CH_2), 60.6 (CH), 53.9 (CH_3), 53.6/53.2 (CH_2), 52.5 (CH_3), 52.4 (CH_3), 39.9 (C), 38.9/38.8 (CH_2), 28.2 (CH_2), 24.5/24.4 (CH_3), 22.3/21.9 (CH_3), 20.9 (CH_3). HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{19}H_{32}N_2O_9Na$ 455.2006; found 455.2002. Anal. calcd for $C_{19}H_{32}N_2O_9$: C, 52.77; H, 7.46; N, 6.48. Found: C, 52.81; H, 7.60; N, 6.47.

*Methyl (2S,4R)-1-[(S)-3-[(Acetoxymethyl)(methoxycarbonyl)-amino]-5-methoxy-4,4-dimethyl-5-oxopentyl]-4-hydroxypyrrolidine-2-carboxylate (**46**).* Obtained from aldehyde **38** (45.5 mg, 0.15 mmol) according to the reductive amination procedure (16 h) using 4-*trans*-hydroxyproline methyl ester hydrochloride as a reagent (31 mg, 0.17 mmol). After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 30:70), yielding diamine **46** (42 mg, 65%, R_f = 0.18) as a viscous oil: $[\alpha]_D^{20}$ −47 (*c* 0.17, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3347, 1722, 1573, 1260, 1157 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 26 °C): δ 5.38 (d, *J* = 11.0 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.50 (br b, 1H), 4.37−4.31 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.48−3.30 (m, 2H), 2.75−2.64 (m, 1H), 2.47−2.37 (m, 1H), 2.33−2.24 (m, 1H), 2.15−2.05 (m, 1H), 2.03 (s, 3H), 2.04−1.94 (m, 1H), 1.90−1.65 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 125.7 MHz, 26 °C): δ 178.1 (C), 175.4 (C), 172.0 (C), 159.3 (C), 70.6 (CH_2), 70.5 (CH), 65.9 (CH), 62.3 (CH_2), 60.6 (CH), 53.9 (CH_3), 53.6 (CH_2), 52.6 (CH_3), 52.4 (CH_3), 39.94 (CH_2), 39.90 (C), 28.2 (CH_2), 24.5 (CH_3), 21.9 (CH_3), 20.9 (CH_3). HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{19}H_{32}N_2O_9Na$ 455.2006; found 455.1991. Anal. calcd for $C_{19}H_{32}N_2O_9$: C, 52.77; H, 7.46; N, 6.48. Found: C, 52.51; H, 7.52; N, 6.20.

General Procedure for the Horner−Wadsworth−Emmons Reaction for the Synthesis of Peptides with Dehydroamino Acid Units. To a solution of the α-phosphonate (0.05 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of tetramethylguanidine (16 μL, 14.5 mg, 0.125 mmol) in dry CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 10 min, and then, the aldehyde (0.1 mmol) in dry CH_2Cl_2 (0.5 mL) was added. After stirring for 16 h, the solution was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, filtered, and evaporated under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc) affording the peptides with dehydroamino acid units **49**−**51**.

*(Z,R)-N-[5-((Acetoxymethyl)(methoxycarbonyl)amino)-2-(N-benzoyl-O-benzyl-L-seryl)amino-2-octenoyl]-L-leucine Methyl Ester (**49**).* Obtained using aldehyde **34** (24.5 mg, 0.1 mmol) and phosphonate **47** (31 mg, 0.05 mmol)[1a] according to the general procedure for the Horner−Wadsworth−Emmons reaction. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 50:50), yielding peptide **49** (30 mg, 85%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ −23 (*c* 0.52, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3413, 3337, 1734, 1705, 1655, 1508, 1481, 1241, 1015 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.88 (br s, 1H), 7.81 (d, *J* = 7.0 Hz, 2H), 7.52 (dd, *J* = 7.5, 7.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 7.5 Hz, 2H), 7.38−7.28 (m, 5H), 7.07 (d, *J* = 6.0 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.52 (t, *J* = 7.5 Hz, 1H), 5.27 (s, 2H), 4.82 (ddd, *J* = 6.0,

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6.0, 5.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.66−4.61 (m, 1H), 4.10 (dd, J = 9.7, 4.7 Hz, 1H), 3.98−3.92 (m, 1H), 3.84 (dd, J = 9.5, 6.5 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.50−2.40 (m, 1H), 2.30 (ddd, J = 15.5, 6.6, 6.5 Hz, 1H), 2.00 (s, 3H), 1.63−1.69 (m, 2H), 1.62−1.54 (m, 2H), 1.50−1.39 (m, 1H), 1.35−1.20 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.0 Hz, 3H), 0.87 (dd, J = 7.5, 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C): δ 173.2 (C), 170.6 (C), 169.1 (C), 167.7 (C), 163.6 (C), 156.8 (C), 139.3 (C), 137.5 (C), 133.6 (C), 132.0 (CH), 131.4 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 127.9 (2 × CH), 127.3 (2 × CH), 73.8 (CH_2), 70.2 (CH_2), 69.4 (CH_2), 57.2 (CH), 54.2 (CH), 53.0 (CH_3), 52.0 (CH_3), 51.4 (CH), 41.6 (CH_2), 35.6 (CH_2), 32.5 (CH_2), 24.9 (CH), 22.7 (CH_3), 22.0 (CH_3), 20.9 (CH_3), 19.6 (CH_2), 13.7 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{37}H_{50}N_4O_{10}Na$ 733.3425; found 733.3433. Anal. calcd for $C_{37}H_{50}N_4O_{10}$: C, 62.52; H, 7.09; N, 7.88. Found: C, 62.67; H, 7.11; N, 8.01.

*(Z,S)-N-[5-((Acetoxymethyl)(methoxycarbonyl)amino)-2-(N-benzoyl-O-benzyl-L-seryl)amino-2-octenoyl]-L-leucine Methyl Ester (**50**).* Obtained from aldehyde **35** (24.5 mg, 0.1 mmol) and phosphonate **47** (31 mg, 0.05 mmol)[1a] according to the general procedure for the Horner−Wadsworth−Emmons reaction. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 50:50), yielding peptide **50** (31 mg, 87%, R_f = 0.10) as a viscous oil: $[\alpha]_D^{20}$ −28 (c 0.68, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3410, 3336, 1735, 1705, 1653, 1515, 1481, 1241, 1015 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 7.90 (br s, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.51 (dd, J = 7.5, 7.0 Hz, 1H), 7.42 (dd, J = 8.0, 7.5 Hz, 2H), 7.40−7.27 (m, 5H), 7.05 (d, J = 6.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.52 (t, J = 7.3 Hz, 1H), 5.26 (d, J = 11.0 Hz, 1H), 5.24 (d, J = 11.5 Hz, 1H), 4.79 (dt, J = 6.0, 5.5 Hz, 1H), 4.69 (d, J = 12.5 Hz, 1H), 4.65−4.61 (m, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.07 (dd, J = 9.5, 5.0 Hz, 1H), 4.00−3.93 (m, 1H), 3.85 (dd, J = 9.7, 6.2 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.51−2.41 (m, 1H), 2.30 (dt, J = 15.5, 6.5 Hz, 1H), 1.99 (s, 3H), 1.72−1.62 (m, 2H), 1.61−1.50 (m, 2H), 1.50−1.38 (m, 1H), 1.35−1.20 (m, 2H), 0.90 (d, J = 6.0 Hz, 3H), 0.87 (dd, J = 8.0, 7.0 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 70 °C) δ 173.3 (C), 170.6 (C), 169.0 (C), 167.8 (C), 163.6 (C), 156.7 (C), 139.3 (C), 137.4 (C), 133.4 (C), 132.1 (CH), 131.7 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 127.9 (2 × CH), 127.3 (2 × CH), 73.7 (CH_2), 70.2 (CH_2), 69.2 (CH_2), 57.1 (CH), 54.3 (CH), 53.0 (CH_3), 52.1 (CH_3), 51.2 (CH), 41.5 (CH_2), 35.5 (CH_2), 32.3 (CH_2), 24.8 (CH), 22.7 (CH_3), 21.9 (CH_3), 20.9 (CH_3), 19.6 (CH_2), 13.7 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{37}H_{50}N_4O_{10}Na$ 733.3425; found 733.3428. Anal. calcd for $C_{37}H_{50}N_4O_{10}$: C, 62.52; H, 7.09; N, 7.88. Found: C, 62.83; H, 7.20; N, 7.65.

*(Z,R)-5-[(Acetoxymethyl)(methoxycarbonyl)amino]-2-(N-benzoyl-O-benzyl-L-seryl)amino-7-oxo-7-phenyl-hept-2-enoate Methyl Ester (**51**).* Obtained using aldehyde **36** (32 mg, 0.1 mmol) and phosphonate **48** (25 mg, 0.05 mmol)[1a] according to the general procedure for the Horner−Wadsworth−Emmons reaction. After work-up and solvent evaporation, the residue was purified by radial chromatography (hexanes/EtOAc, 50:50), yielding peptide **51** (28 mg, 83%, R_f = 0.08) as a viscous oil: $[\alpha]_D^{20}$ +13 (c 0.73, $CHCl_3$). IR ($CHCl_3$) ν_{max}: 3412, 3314, 1715, 1660, 1481, 1258, 1017 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 70 °C) rotamer equilibrium. Two sets of signals at 26 °C, one set at 70 °C: δ 8.11 (s, 1H), 7.88 (d, J = 7.0 Hz, 2H), 7.84 (d, J = 7.0 Hz, 2H), 7.54 (dd, J = 7.5, 7.0 Hz, 1H), 7.50 (dd, J = 7.5, 7.0 Hz, 1H), 7.42 (dd, J = 8.0, 7.5 Hz, 4H), 7.35−7.24 (m, 5H), 7.14 (d, J = 6.5 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.44 (d, J = 11.0 Hz, 1H), 5.31 (d, J = 11.0 Hz, 1H), 4.93 (dt, J = 6.7, 4.3 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.56−4.40 (m, 1H), 4.10 (dd, J = 9.5, 4.0 Hz, 1H), 3.79 (dd, J = 9.5, 7.0 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.63−3.48 (m, 1H), 3.10 (dd, J = 17.5, 6.0 Hz, 1H), 2.86−2.67 (m, 1H), 2.53 (ddd, J = 15.5, 7.5, 6.1 Hz, 1H), 1.92 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125.7 MHz, 26 °C): δc 197.5 (C), 170.6 (C), 168.9 (C), 167.4 (C), 164.2 (C), 155.5 (C), 137.6 (C), 136.5 (C), 133.7 (C), 133.6 (C), 133.4 (CH), 131.9 (CH), 128.64 (2 × CH), 128.59 (CH), 128.5 (4 × CH), 128.0 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 127.2 (2 × CH), 73.6 (CH_2), 73.1 (CH_2), 69.3 (CH_2), 58.8 (CH), 55.0 (CH), 53.1 (CH_3), 52.4 (CH_3), 41.8 (CH_2), 31.8 (CH_2), 20.8 (CH_3). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{36}H_{39}N_3O_{10}Na$ 696.2533; found 696.2532. Anal. calcd for $C_{36}H_{39}N_3O_{10}$: C, 64.18; H, 5.84; N, 6.24. Found: C, 64.36; H, 5.78; N, 6.57.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02751.

Procedures for the preparation of new substrates **8**, **16**, **18**, **19**, **22**, and **27**−**33** and products **10**−**14**, **20**, **21**, **23**−**26**, and **34**−**51**; their reproduction of ^1H and ^{13}C NMR spectra; and NOESY and heteronuclear single quantum coherence (HSQC) experiments of compounds **49**−**51** (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DIB, (diacetoxyiodo)benzene; DCM, dichloromethane; Hyp, hydroxyproline; MeOH, methanol; EtOAc, ethyl acetate

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