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An Efficient Enantioselective Approach to Cyclic β-Amino Acid Derivatives via Olefin Metathesis Reactions

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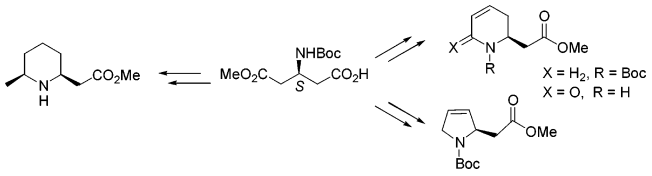

The asymmetric synthesis of polyfunctionalized piperidine- and pyrrolidine-based scaffolds, specifically designed for the preparation of cyclic, conformationally constrained β-amino acids, is realized combining a biocatalytic access to a versatile chiral building block with a wide range of transformations based on olefin metathesis.

The β-amino acids have aroused considerable attention due to their important biological properties in drugs and natural products.[1] They are found, for instance, in the anticancer agent Taxol, macrocyclic peptides, and β-lactams. Furthermore, they are useful tools in the synthesis of modified peptides and peptidomimetics.[2] Particularly, the incorporation of conformationally constrained β-amino acids (β-AAs) is a well-established strategy to increase the stability of peptides to enzymatic degradation and to reduce the inherent flexibility of the peptide backbone, improving the ability to adopt stable secondary structures in solution.[3] β-Peptides are relevant in biological studies to investigate the topology of receptors and also are prominent candidates in the development of orally active new drugs. In most cases, constraint in these amino acids is induced by the presence of a small or midsized ring as a structural feature. Thanks to their conformational stability, of particular interest are those C^3-monosubtituted β-amino acids (β^3-AAs) which incorporate the amino group in a heterocyclic ring. For these reasons, some methods for the synthesis of this type of cyclic β^3-amino acids in optically active form have been developed, the majority of which based on homologation of α-amino acids. Arndt−Eistert homologation of (*S*)-proline has been used to access homoproline[4] and homopipecolic acid.[5] An elegant approach from Enders et al.[6] carried out conjugate addition of lithiated TMS-SAMP to ω-halide-substituted enoates, leading to the synthesis of cyclic β^3-AAs via Michael addition followed by ring closure. Quite recently, advances in the enantioselective synthesis of β-AAs have been extensively reviewed.[7]

One possible approach to the synthesis of nitrogen heterocycles involves the olefin metathesis reaction,[8] widely used in the recent past as a result of the development of highly stable and active ruthenium alkylidenes catalysts.

As part of our ongoing project on the asymmetric synthesis of nitrogen compounds by metathesis reactions,[9] here we report a versatile method for the preparation of a range of functionalized cyclic β-amino acid derivatives (**1**−**4**), based on ring-closing metathesis (RCM) and cross metathesis (CM) reactions. The keys to our strategy are the enzymatic asymmetrization of dimethyl-*N*-Boc-3-aminoglutarate and the employment of the resulting chiral monoacid **5** as the centerpiece of different metathesis-based synthetic routes (Scheme 1).

In line with literature precedents,[10] dimethyl-*N*-Boc-3-aminoglutarate was prepared from commercially available dimethyl 2-oxoglutarate and subsequently desymmetrized by means of enantioselective hydrolysis with pig liver esterase. The chiral synthon **5** could be obtained in 96% yield on multigram scale, with >96% ee and 3*S* configuration[11] (Scheme 2).

Preparations of the key dienes **6**−**8** from monoacid monoester **5** are shown in Scheme 3, pathways A, B, and C, respectively.

The syntheses began with selective reduction of the carboxylic group of **5** with BH_3·THF to give the alcohol **9** in quantitative yield. Subsequent oxidation to aldehyde **10** proceeded smoothly under Swern conditions, followed by standard Wittig reaction

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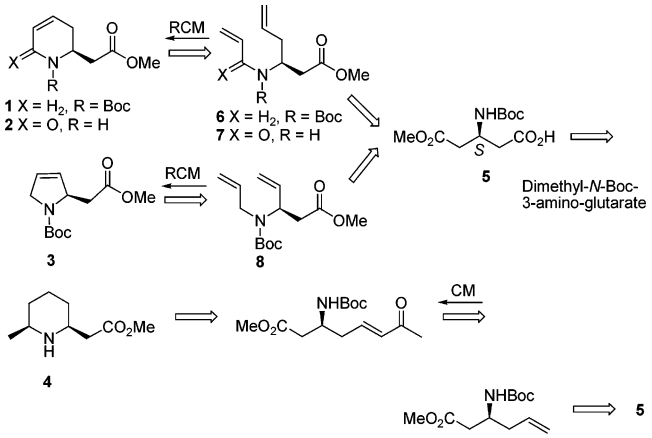
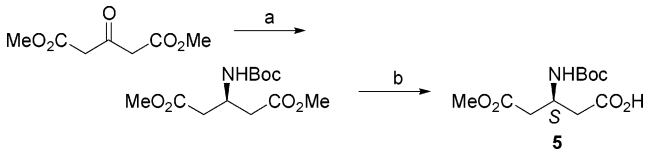
SCHEME 1. Retrosynthetic Analysis

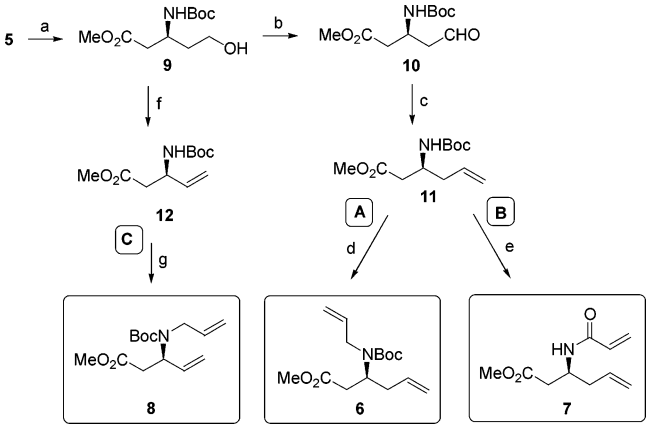


SCHEME 2[a]



[a] Conditions: (a) (i) $AcONH_4$, 3 Å mol. sieves, AcOH, $NaCNBH_3$, MeOH, 70%, (ii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 78%; (b) PLE, phosphate buffer (0.5 M, pH 8), acetone, 96%.

SCHEME 3[a]

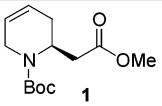
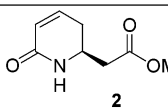
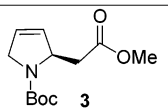


[a] Conditions: (a) 1 M BH_3·THF, THF, −78 °C, 98%; (b) Swern oxid, 93%; (c) $(MePh_3P)^+I^-$, $(Me_3Si)_2N^-K^+$, THF, 0 °C, 85%; (d) allyl iodide, $(Me_3Si)_2N^-K^+$, DMF, 0 °C, 75%; (e) (i) TFA, CH_2Cl_2, (ii) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 79% overall; (f) (i) *o*-NO_2Ph selenocyanate, Bu_3P, THF, 70%, (ii) $NaIO_4$, MeOH/H_2O, 0 °C, 86%; (g) allyl iodide, $(Me_3Si)_2N^-K^+$, DMF, 0 °C, 69%.

with methyltriphenylphosphonium iodide affording **11** in 79% overall yield. Alkylation of **11** worked efficiently, in the presence of potassium bis(trimethylsilyl)amide and allyl iodide, but the desired diene **6** needed to be separated from small amounts of the competitive Cα-alkylation product. We next prepared diene **7** from **11** via Boc deprotection and acylation with acryloyl chloride and TEA in CH_2Cl_2 (79% yield for the two steps).

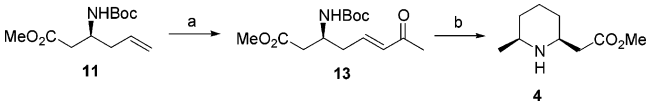
From alcohol **9**, conversion into the terminal olefin **12** was achieved by a standard Grieco−Sharpless protocol. Reaction with *o*-nitrophenyl selenocyanate afforded the corresponding *o*-nitrophenyl selenide which was directly oxidized with peri-

TABLE 1. Ru-Catalyzed RCM Reactions

Diene	Product	Catalyst[a]	Yield[b]
6	 **1**	**A** (rt) **B** (rt)	79 85
7	 **2**	**A** (reflux) **B** (rt)	45 92
8	 **3**	**A** (reflux) **B** (rt)	60 89

[a] All reactions were carried out in CH_2Cl_2. [b] Isolated yield after chromatography.

SCHEME 4[a]



[a] Conditions: (a) methyl vinyl ketone, 5 mol % **C**, CH_2Cl_2, rt, 75%; (b) 3 M HCl/MeOH, then H_2, Pd/C, 52%.

date, yielding **12** in overall 60% yield. Alkylation of **12** was performed as for **11**, thus providing diene **8** in 69% yield.

With the β-amino esters properly functionalized **6**−**8** in hand, we next examined ring-closing metathesis (RCM) conditions to achieve the cyclic β-amino esters **1**−**3**, respectively, and the results are summarized in Table 1. RCM reactions were carried out using commercially available Grubbs' ruthenium catalysts, that is the less expensive first-generation benzylidenebis(tricyclohexylphosphine)dichlororuthenium **A** and the recent second-generation benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)-ruthenium **B**, in CH_2Cl_2 at rt or at reflux. In all cases, ring closure proceeded smoothly with 5% mol of catalyst and yields ranging from 45 to 92%. It is worth noting that the diene **6** cyclized equally well in the presence of **A** or **B** at rt to give the six-membered cyclic β-amino ester **1** in high yield. However, in the case of **7**, rt and refluxing conditions with **A** did not work as well, while almost quantitative yield of the cyclic product **2** was obtained with **B** at rt. Finally, diene **8** cyclized readily both with **A** at reflux and with **B** at rt, thus affording the 2,5-dihydropyrrole derivative **3**,[12] which was recently described as an intermediate in the synthesis of some peptidomimetic inhibitors of CAC1 cysteinyl proteinases.[13]

We have also briefly investigated the efficiency of a CM methodology in order to access 2,6-*cis*-disubstituted piperidines from *N*-protected homoallylic amine **11** (Scheme 4). This approach relies on an highly selective cross-coupling reaction

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of **11** with an α,β-unsatured ketone, followed by *N*-deprotection and reductive cyclization.

The CM reaction was carried out first between **11** and methyl vinyl ketone in CH_2Cl_2 at rt utilizing catalysts **A** and **B** up to 10 mol %. In all cases, both coupling partners were reacted in a 1:1 ratio, giving exclusively the *E*-configurated alkene **13** in moderate yields. The efficiency of the reaction improved considerably when the more highly active Hoveyda−Grubbs second-generation (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium **C** was employed. This catalyst, which is well suited to electron-deficient substrates, increased the yield of **13** to 75%, when the reaction was performed at rt. Alkene **13** was stirred in a 3 M HCl/MeOH solution for 6 h and then placed under hydrogen for 12 h, with 10% mol Pd/C. Hydrogenation of the intermediate iminium ion took place from the least hindered face, and the 2*S*,6*R*-*cis*-substituted piperidine **4** was formed exclusively. The *cis* stereochemistry was unambiguously assigned by comparison with NMR literature values for **4** as chloridrate salt.[14]

In conclusion, a straightforward strategy involving metathesis reactions starting from a common chiral intermediate has been successfully developed. Application of this protocol permits the asymmetric synthesis of heterocyclic β-amino acids derivatives **1**−**4**, which are suitably protected for solid-phase application. Additionally, the double bond in **1**−**3** provides a useful chemical handle for alternative functionalization chemistries. We are currently examining further variations of this methodology, as well as applications to the synthesis of other heterocyclic systems.

Experimental Section

3*S*-*tert*-Butoxycarbonylaminopentanedioic Acid Monomethyl Ester 5. To a mixture of 3-*tert*-butoxycarbonylaminopentanedioic acid dimethyl ester (1 g, 3.6 mmol) in phosphate buffer (0.5 M, pH 8) (100 mL) and acetone (4 mL) was added pig liver esterase (PLE, 1200 units). The mixture was stirred at 25 °C for 4 h. The pH of the mixture was checked periodically, and 0.1 M NaOH was added by drops, if required, to maintain the pH at 8.0. The resultant solution was acidified to pH 2.0 by the addition of concd aq HCl and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aq NaCl solution and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded 902 mg (96%) of pure **5**, as a colorless oil: $[\alpha]^{25}_D$ −1.50 (*c* 1, $CHCl_3$) [lit.[11] $[\alpha]^{25}_D$ −1.36 (*c* 0.75, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 10.98 (s, br, 1H), 5.40 (m, br, 1H), 4.27 (m, br, 1H), 3.66 (s, 3H), 2.65 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.1, 171.8, 155.2, 79.9, 51.8, 44.1, 37.9, 28.3; HRMS *m*/*z* calcd 261.1212, found 261.1208. Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36; O, 36.74. Found: C, 50.69; H, 7.51; N, 5.11.

3*S*-*tert*-Butoxycarbonylamino-5-hydroxypentanoic Acid Methyl Ester 9. To a solution of **5** (1.6 g, 6.1 mmol) in dry THF (20 mL) under nitrogen at −78 °C, a solution of borane THF complex (1M in THF, 9.2 mL, 9.2 mmol) was added dropwise. The mixture was stirred for 4 h at 0 °C, then a saturated NH_4Cl aqueous solution was added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 3:1) yielded 1.5 g (98%) of **9** as a colorless oil: $[\alpha]^{25}_D$ −23.9 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.38 (m, br, 1H), 4.12 (m, br, 2H), 3.69 (s, 3H), 3.64 (m, br, 2H), 2.65−2.48 (m, 2H), 1.90−1.71 (m, br, 1H), 1.57 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.1, 156.6, 79.9, 66.4, 61.4, 58.7, 51.7, 44.1, 39.0, 37.4, 28.3; HRMS *m*/*z* calcd 247.1420, found 247.1423. Anal. Calcd for $C_{11}H_{21}NO_5$: C, 53.43; H, 8.56; N, 5.66; O, 32.35. Found: C, 53.68; H, 8.29; N, 5.81.

3*S*-*tert*-Butoxycarbonylamino-5-oxopentanoic Acid Methyl Ester 10. To a stirred solution of 2 equiv of oxalyl chloride in 12 mL of anhydrous CH_2Cl_2 under nitrogen at −78 °C was added 3 equiv of anhydrous DMSO in 4 mL of anhydrous CH_2Cl_2 dropwise and the mixture allowed to react for 5 min −78 °C. The alcohol **9** (1 g, 4.0 mmol) in 4 mL of anhydrous CH_2Cl_2 was added, and the reaction mixture was stirred for 1 h at −78 °C. On addition of 4 equiv of anhydrous Et_3N, the reaction temperature was allowed to go to rt. The reaction was diluted with 20 mL of CH_2Cl_2 and then poured into 50 mL of CH_2Cl_2/20 mL of 10% aq NH_4OH solution. The aqueous phase was extracted twice with CH_2Cl_2, and the combined CH_2Cl_2 fractions were dried and evaporated. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:1) yielded 911 mg (93%) of **10** as a colorless oil: $[\alpha]^{25}_D$ −3.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.70 (s, 1H), 5.24 (m, br, 1H), 4.35 (m, 1H), 3.65 (s, 3H), 2.75 (m, 2H), 2.63 (m, 2H), 1.39 (s, 9H); HRMS *m*/*z* calcd 245.1263, found 245.1259. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71; O, 32.61. Found: C, 53.69; H, 7.99; N, 5.76.

3*S*-*tert*-Butoxycarbonylaminohex-5-enoic Acid Methyl Ester 11. To a stirred suspension of $[(Me(Ph)_3P]^+I^-$ (3.4 g, 8.4 mmol) in dry THF (40 mL) under nitrogen at 0 °C was added dropwise a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 16.8 mL, 8.4 mmol). The mixture was stirred for 10 min at 0 °C and then for 20 min at rt. Then the reaction temperature was lowered to −78 °C, and a solution of **10** (1.5 g, 6.3 mmol) in THF dry (10 mL) was added. The reaction was stirred for 3 h at rt, then a saturated NH_4Cl aqueous solution was added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:4) yielded 1.3 g (85%) of **11** as a colorless oil: $[\alpha]^{25}_D$ −4.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.77 (ddt, J = 17.5, 9.6, 7.1 Hz, 1H), 5.11 (m, 2H), 4.97 (m, br, 1H), 2.65 (m, br, 1H), 3.70 (s, 3H), 2.55 (d, J = 5.6 Hz, 2H), 2.32 (m, 2H), 1.45 (s, 9H); HRMS *m*/*z* calcd 243.1471, found 243.1474. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76; O, 26.30. Found: C, 59.36; H, 8.55; N, 5.90.

3*R*-*tert*-Butoxycarbonylaminopent-4-enoic Acid Methyl Ester 12. To a stirred solution of **9** (500 mg, 2.0 mmol) and *o*-nitrophenylselenocyanate (685 mg, 3.0 mmol) in THF (15 mL) was added tributylphosphine (770 μL, 3.0 mmol) under nitrogen at rt. After 2 h, the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:2) yielded 600 mg (70%) of *o*-nitrophenylselenide derivative. To a stirred solution of *o*-nitrophenylselenide derivative (600 mg, 1.4 mmol) in MeOH (20 mL) was added $NaIO_4$ aq solution (0.2 M, 10 mL, 2.0 mmol) dropwise at 0 °C. After 1 h, ether was added and the mixture washed with saturated $NaHCO_3$ aq solution, water, and brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by filtration on silica gel (CH_2Cl_2) yielding 276 mg (86%) of **12**, as a colorless oil: $[\alpha]^{25}_D$ −23.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.81 (ddd, J = 16.6, 11.7, 5.9 Hz, 1H), 5.18 (d, J = 16.6 Hz, 1H), 5.15 (d, br, 1H), 5.10 (d, J = 11.7 Hz, 1H), 4.48 (m, br, 1H), 3.65 (s, 3H), 2.59 (d, J = 5.9 Hz, 2H), 1.45 (s, 9H); HRMS *m*/*z* calcd 229.1314, found 229.1318. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11; O, 27.92. Found: C, 57.97; H, 8.29; N, 6.88.

3*S*-(Allyl-*tert*-butoxycarbonylamino)hex-5-enoic Acid Methyl Ester 6. To a stirred solution of **11** (650 mg, 2.7 mmol) in dry DMF (15 mL) under nitrogen at −20 °C was added dropwise a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 5.9 mL, 2.9 mmol). After 10 min, allyl iodide (498 μL, 5.4 mmol)

(14) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399−5400.

was quickly added and the resulting solution stirred for further 2 h at 0 °C. It was then poured into a 5% H_3PO_4 aq solution which was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:6) yielded 573 mg (75%) of **6**, as a colorless oil: $[\alpha]^{25}_D$ +28.4 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 323 K) δ_H 5.80 (ddt, *J* = 17.1, 9.6, 5.3 Hz, 1H), 5.72 (ddt, *J* = 17.6, 9.6, 6.6 Hz, 1H), 5.17−4.98 (m, 4H), 4.16 (m, br, 1H), 3.85−3.67 (m, 2H), 3.62 (s, 3H), 2.69 (dd, *J* = 14.9, 7.9 Hz, 2H), 2.52 (dd, *J* = 14.9, 6.2 Hz, 2H), 2.43 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H); HRMS *m*/*z* calcd 283.1784, found 283.1788. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94; O, 22.58. Found: C, 63.24; H, 8.79; N, 5.03.

3*S*-Acryloylaminohex-5-enoic Acid Methyl Ester 7. A solution of **11** (394 mg, 1.6 mmol) in CH_2Cl_2/TFA (2:1) (5 mL) was stirred at 0 °C for 30 min, poured into a saturated $NaHCO_3$ aq solution, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. To a stirred solution of the crude amine in dry CH_2Cl_2 (5 mL), TEA (386 μL, 2.8 mmol), DMAP (20 mg, 0.16 mmol), and acryloyl chloride (133 μL, 1.6 mmol) were added under nitrogen at 0 °C. After the mixture was stirred for 12 h at rt, the resulting solution was diluted with CH_2Cl_2, washed with aq 1 M HCl, saturated $NaHCO_3$ aq solution, water, and brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane 2:3) yielding 250 mg (79%) of **7**, as a colorless oil: $[\alpha]^{25}_D$ −7.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.32 (d, br, *J* = 6.8 Hz 1H), 6.23 (dd, *J* = 16.6, 1.9, 1H), 6.06 (dd, *J* = 16.6, 9.8, 1H), 5.72 (ddt, *J* = 16.6, 9.8, 6.8 Hz, 1H), 5.60 (dd, *J* = 9.8, 1.9, 1H), 5.06 (d, br *J* = 11.7 Hz, 2H), 4.42−4.29 (m, 1H), 3.65 (s, 3H), 2.56 (d, *J* = 4.9 Hz, 2H), 2.43−2.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 172.8, 165.5, 134.5, 131.5, 127.1, 118.9, 52.3, 46.3, 38.9, 37.9; HRMS *m*/*z* calcd 197.1052, found 197.1055. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10; O, 24.34. Found: C, 61.01; H, 7.51; N, 7.24.

3*R*-(Allyl-*tert*-butoxycarbonylamino)pent-4-enoic Acid Methyl Ester 8. To a stirred solution of **12** (200 mg, 0.9 mmol) in DMF dry (5 mL) under nitrogen at −20 °C was added dropwise a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 2.0 mL, 1.0 mmol). After 10 min, allyl iodide (166 μL, 1.8 mmol) was quickly added and the resulting solution stirred for further 2 h at 0 °C. It was then poured into a 5% H_3PO_4 aq solution, which was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:6) yielded 167 mg (69%) of **6**, as a colorless oil: $[\alpha]^{25}_D$ +42.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.94−5.71 (m, 2H), 5.14 (m, 2H), 5.08 (m, 2H), 4.75 (m, br, 1H), 3.87 (m, br, 1H), 3.72 (m, 1H), 3.68 (s, 3H), 2.79 (dd, *J* = 15.2, 7.6, 1H), 2.69 (dd, *J* = 15.2, 7.2 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.0, 155.6, 137.2, 135.9, 116.7, 80.6, 56.5, 52.1, 49.0, 38.3, 29.0; HRMS *m*/*z* calcd 269.1627, found 269.1630. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20; O, 23.76. Found: C, 62.28; H, 8.49; N, 5.31.

2*S*-Methoxycarbonylmethyl-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester 1. To a solution of **6** (510 mg, 1.8 mmol) in CH_2Cl_2 (30 mL) was added Ru-catalyst **B** (Grubbs secondnd generation) (5% mol) under nitrogen, and the solution was stirred for 2 h. The solvent was then evaporated and the residue purified by flash chromatography on silica gel (ethyl acetate/hexane 1:8) yielding 390 mg (85%) of **1**, as a colorless oil: $[\alpha]^{25}_D$ +28.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.70 (m, br, 2H), 4.71 (m, br, 1H), 4.21 (d, br, *J* = 18.6 Hz, 1H), 3.67 (s, 3H), 3.58 (d, br, *J* = 18.6 Hz, 1H), 2.59−2.41 (m, 3H), 1.90 (d, br *J* = 17.1 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (two distinct conformers) δ_C 171.8, 154.6, 123.5, 121.1, 79.8, 51.9, 46.0 and 44.7, 40.4 and 39.0, 36.6, 28.8, 28.3; HRMS *m*/*z* calcd 255.1471, found 255.1465. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49; O, 25.06. Found: C, 61.01; H, 8.61; N, 5.44.

2*S*-(6-Oxo-1,2,3,6-tetrahydropyridin-2-yl)acetic Acid Methyl Ester 2. To a solution of **7** (400 mg, 2.0 mmol) in CH_2Cl_2 (35 mL) was added Ru-catalyst **B** (Grubbs second generation) (5% mol) under nitrogen, and the solution was stirred for 4 h. The solvent was then evaporated and the residue purified by flash chromatography on silica gel (ethyl acetate) yielding 311 mg (92%) of **2**, as a colorless oil: $[\alpha]^{25}_D$ +21.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.59 (dt, *J* = 9.9, 4.1 Hz, 1H), 6.29 (s, 1H), 5.93 (d, br, *J* = 9.9 Hz, 1H), 4.03 (m, 1H), 3.72 (s, 3H), 2.67 (dd, *J* = 16.3, 8.7 Hz, 1H), 2.58 (m, 2H), 2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.8, 166.4, 140.2, 125.4, 54.1, 48.1, 40.3, 29.8; HRMS *m*/*z* calcd 169.0739, found 169.0743. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28; O, 28.37. Found: C, 56.55; H, 6.71; N, 8.31.

2*R*-Methoxycarbonylmethyl-2,5-dihydropyrrole-1- carboxylic Acid *tert*-Butyl Ester 3. To a solution of **8** (208 mg, 0.8 mmol) in CH_2Cl_2 (15 mL) was added Ru-catalyst **B** (Grubbs second generation) (5% mol) under nitrogen, and the solution was stirred for 4 h. The solvent was then evaporated and the residue purified by flash chromatography on silica gel (ethyl acetate) yielding 172 mg (89%) of **3**, as a colorless oil: $[\alpha]^{25}_D$ −203.0 (*c* 1, $CHCl_3$) [lit.[12a] $[\alpha]^{25}_D$ −189 (*c* 1, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.82 (m, br, 2H), 4.79 (m, br, 1H), 4.14 (m, br, 1H), 4.02 (dd, *J* = 15.5, 5.4 Hz, 1H), 3.68 (s, 3H), 3.00 (m, br, 1H), 2.45 (m, br, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) (two distinct conformers) δ_C 171.5, 153.8, 129.3, 125.7, 79.9 and 79.4, 60.8 and 60.5, 53.4 and 51.3, 51.2, 39.2 and 38.2, 28.1; HRMS *m*/*z* calcd 241.1314, found 241.1311. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.91; H, 8.19; N, 5.77.

3*S*-*tert*-Butoxycarbonylamino-7-oxooct-5-enoic Acid Methyl Ester 13. To a solution of **11** (200 mg, 0.8 mmol) and methyl vinyl ketone (67 μL, 0.8 mmol) in CH_2Cl_2 (0.05 M, 16 mL) was added Ru-catalyst C (Hoveyda−Grubbs second Generation) (5% mol) under nitrogen, and the solution was stirred for 12 h. The solvent was then evaporated and the residue purified by flash chromatography on silica gel (ethyl acetate/hexane 2:3) yielding 195 mg (75%) of **13**, as a colorless oil: $[\alpha]^{25}_D$ +9.2 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.71 (dt, *J* = 16.6, 6.8 Hz, 1H), 6.06 (d, *J* = 16.6 Hz, 1H), 5.10 (d, *J* = 7.8 Hz, 1H), 4.08 (m, 1H), 3.66 (s, 3H), 2.53 (t, br, *J* = 4.8 Hz, 2H), 2.45 (t, br, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 198.9, 172.3, 155.8, 144.0, 134.4, 80.4, 52.5, 47.4, 39.1, 38.4, 29.0, 27.5; HRMS *m*/*z* calcd 285.1576, found 285.1570. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91; O, 28.04. Found: C, 58.61; H, 8.44; N, 5.08.

(2*S*,6*R*)-(6-Methyl-piperidin-2-yl)acetic Acid Methyl Ester 4. Compound **13** (190 mg, 0.6 mmol) was dissolved in a 3 N HCl methanolic solution (5 mL) and stirred for 6 h at rt, then Pd/C 10% (20 mg) was added, and the mixture was further stirred under H_2 atmosphere for 12 h. The catalyst was filtered, the solvent was evaporated to yield 65 mg (52%) of pure **4**, as hydrochloride salt: $[\alpha]^{25}_D$ +13.8 (*c* 1, MeOH) [lit.[14] $[\alpha]^{25}_D$ +14.5 (*c* 0.8, MeOH)]; ^{1}H NMR (300 MHz, MeOH) δ_H 3.70 (s, 3H), 3.65−3.56 (m, 2H), 3.15−3.11 (m, 1H), 2.92−2.88 (m, 1H), 2.00−1.70 (m, 6H), 1.55 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75.4 Hz, MeOH) δ_C 170.5, 54.2, 54.0, 52.3, 37.5, 31.0, 28.3, 22.6, 19.3; HRMS *m*/*z* calcd 171.1259, found 171.1263. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18; O, 18.69. Found: C, 63.55; H, 8.58; N, 18.21.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**3** and **5**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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