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Synthesis of Cyclic β-Amino Acid Esters from Methionine, Allylglycine, and Serine

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Here we report a versatile ring-closing metathesis-based approach to 5-, 6-, and 7-membered cyclic β-amino esters starting with simple and readily available building blocks—methionine, allylglycine, and serine—where the nature of the amino acid determines the size of the carbocyclic ring.

Introduction

β-Peptides are biologically and structurally important oligomers of β-amino acids that possess a high resistance to peptidase hydrolysis[1,2] and an ability to adopt stable secondary structures such as helices, sheets, and turns.[3,4] For example, oligomers of *trans*-2-aminocyclopentanecarboxylic acid **1** and *trans*-aminocyclohexanecarboxylic acid **2** have recently been shown by Gellman and co-workers to form 14- and 12-helices that are generally more rigid and stable than those comprised of linear α- and β-amino acids (Figure 1).[5−7] Furthermore, modification of the carbocyclic ring of these monomeric units to include additional functional groups has led to foldamers with enhanced solubility in aqueous media.[8] As such, β-peptides have promise as a new class of medicinal agents with application to the generation of inhibitors of a range of biological processes.[2,9−11]

A number of methods have been reported for the preparation of cyclic β-amino acids,[7,12−19] the majority of which employ an enzymatic resolution or chemoselective resolution as a key step. Recently, several enantioselective syntheses have also been reported.[20−25] Here, we report a versatile method for the preparation of a range of functionalized cyclic β-amino esters from simple and readily available building blocks—methionine, allylglycine, and serine—where the nature of the amino acid starting material determines the size of the carbocyclic ring. The key to our strategy is the diastereoselective preparation of dienes of type **6** (Figure 2), which cyclize in the presence of catalysts **3** or **4** to give cyclopentenyl, cyclohexenyl,[26] and cycloheptenyl-based β-amino esters

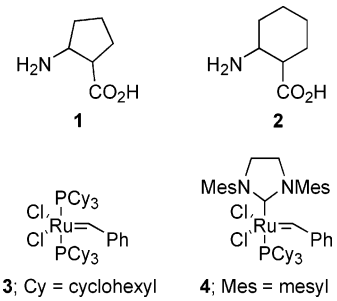

FIGURE 1. Cyclic β-amino acids and RCM catalysts.

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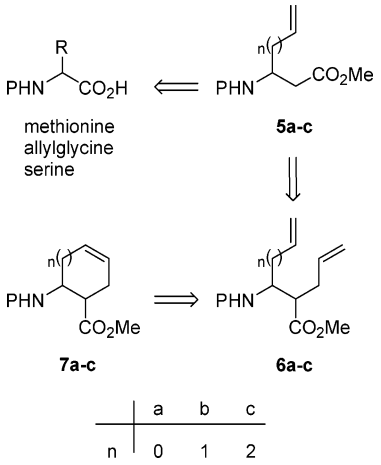


FIGURE 2. Retrosynthetic analysis.

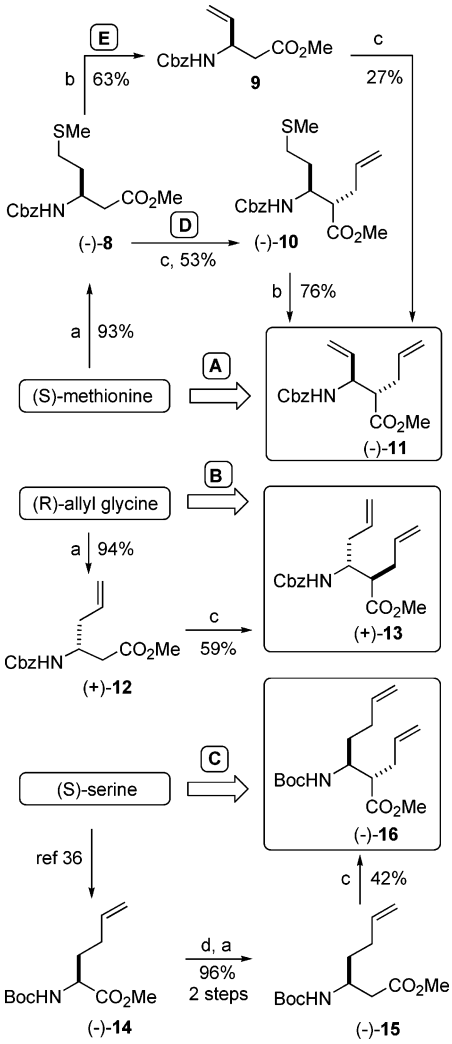
of type **7**. There are few reports on 7-membered cyclic *β*-amino esters, and their related acids, of the type reported here.[12,27]

Results and Discussion

Preparations of the key unsubstituted dienes of type **6**, specifically (−)-**11**, (+)-**13**, and (−)-**16**, from the amino acids (*S*)-methionine, (*R*)-allyl glycine, and (*S*)-serine are shown in Scheme 1, pathways **A**, **B**, and **C**, respectively. The syntheses begin with an Arndt−Eistert homologation of the appropriate α-amino acid[28] to give the corresponding *β*-amino acid, which is stereoselectively allylated to introduce one of the olefinic groups of the diene, the second being derived from the amino acid R group. The R groups of the serine- and methionine-based examples provide a masked alkene that is liberated at the appropriate time in the synthesis to give the required diene. Natural (*S*)-methionine and (*S*)-serine were used in the preparation of (−)-**11** and (−)-**16**, while (*R*)-allylglycine was used to prepare (+)-**13**. A second series of α-substituted dienes (−)-**19**, (±)-**21**, and (±)-**22** were also prepared in an analogous fashion by carrying out a second alkylation step as shown in Schemes 2 and 3.

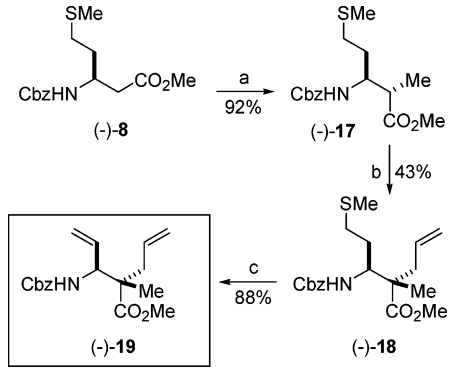
Thus, (3*R*)-3-benzyloxycarbonylamino-5-methylsulfanylpentanoic acid methyl ester (−)-**8** was prepared from Cbz-protected methionine in 93% yield over two steps (Scheme 1). Conversion to diene (−)-**11** then required oxidative elimination of the methylsulfanyl side chain and an allylation α to the ester group. In the first instance, we found that oxidation of the methylsulfanyl group of (−)-**8**, using hydrogen peroxide in acetic acid, followed by thermal elimination, at 200 °C in xylene in a sealed tube,[29,30] gave the vinyl *β*-amino acid methyl ester **9** in 63% yield (Scheme 1, pathway **D**). Subsequent alkylation of **9**, in the presence of LDA and allyl bromide, gave the optically active diene (−)-**11** as a single diastereoisomer[31] by ^{1}H NMR spectroscopy, in 27% yield. However, a reversal in the order of the steps, i.e., allylation followed by oxidative elimination (pathway **E**), gave an improved yield of the required diene. In particu-

SCHEME 1[a]



[a] Reagents and conditions: (a) (i) Et_3N, $ClCO_2Et$, THF, −15 °C, 15 min; (ii) CH_2N_2, 0 °C; (iii) AgBz, Et_3N, MeOH, −25 °C; (b) (i) H_2O_2, AcOH, rt 4 h, (ii) xylene 200 °C, sealed tube; (c) LiCl, 2 equiv of LDA, allyl bromide, THF, −78 °C; (d) NaOH, MeOH, reflux.

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) LiCl, 2 equiv of LDA, THF, −78 °C, MeI; (b) LiCl, 2 equiv of LDA, THF, −78 °C, allyl bromide, (c) (i) H_2O_2, AcOH, rt 15 min, (ii) xylene, 200 °C, sealed tube.

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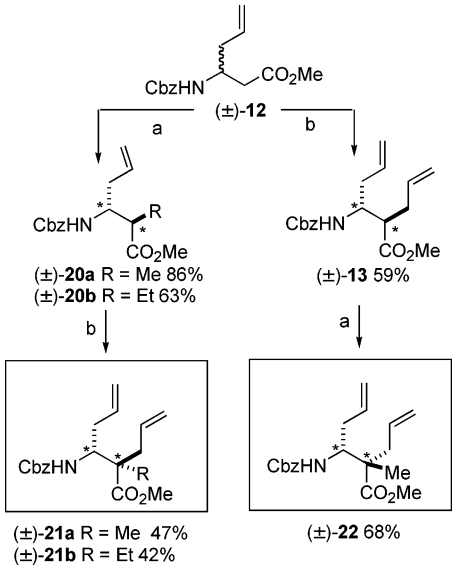
SCHEME 3[a]



[a] Reagents and conditions: (a) (i) LiCl, 2 equiv of LDA, THF, −78 °C, MeI or EtI; (b) LiCl, 2 equiv of LDA, THF, −78 °C, allyl bromide.

lar, alkylation of (−)-**8** in the presence of LDA and allyl bromide gave (−)-**10** as a single diastereoisomer by ^{1}H NMR spectroscopy,[31] in 53% yield. Oxidation and thermal elimination of the methylsulfanyl group of (−)-**10** proceeded cleanly to give diene (−)-**11** in 76% yield after chromatography (41% yield from (−)-**8**). An optical rotation of −37° was obtained for samples of (−)-**11** prepared by pathways **D** and **E**.

In a preliminary communication, we reported the synthesis of diene (+)-**13** in >95% ee from optically active (+)-**12**, itself obtained by Evan's chiral auxiliary chemistry.[26] We now report full details for the conversion of (+)-**12** to (+)-**13** and an alternative method for the preparation of (+)-**12** from optically active allylglycine via an Arndt−Eistert homologation—a method analogous to that described for (−)-**10** above. We also report full details for the RCM cyclization of (+)-**13** to the six-membered cyclic amino acid (−)-**24**. (*R*)-Allyglycine was obtained commercially and by asymmetric allylation of a chiral Ni(II)−glycine complex using the method of Belokon et al.[32−35] Stereoselective alkylation of (+)-**12** with allyl bromide gave (+)-**13** as a single diastereoisomer by ^{1}H NMR spectroscopy,[31] in 59% yield after purification, the data for which was consistent with that obtained previously.[26]

The diene (−)-**16** was prepared from (*S*)-serine using the general method described for the preparation of (−)-**11** and (+)-**13**—allylation of 3-*tert*-butoxycarbonylamino-hept-6-enoic acid methyl ester (−)-**15** gave diene (−)-**16**, as a single diastereoisomer by ^{1}H NMR spectroscopy,[31] in 42% yield after chromatography. The key starting α-amino ester, *N*-Boc-but-3-enylglycine methyl ester (−)-**14**, was obtained in 82% yield from *N*-Boc-(*S*)-serine methyl ester, via reaction of the corresponding iodide with zinc dust and allyl chloride in the presence of CuBr·SMe_2.[36] Hydrolysis of the methyl ester of (−)-**14**, followed by C-terminus extension using Ardnt−Eistert methodology, gave (−)-**15** in 92% yield over two steps. It is worth noting that the enantiomer (+)-**15** can be similarly prepared from (*S*)-aspartic acid.[37]

With the α-substituted *β*-amino ester dienes in hand, we next demonstrated an ability to prepare α,α-disubstituted dienes in which a second substituent is introduced stereoselectively at the α-position; see Schemes 2 and 3 for the preparation of α,α-disubstituted dienes (−)-**19**, (±)-**21a**, (±)-**21b**, and (±)-**22**. Here, alkylation of (−)-**8** (prepared as shown in Scheme 1) with methyl iodide gave the α-methyl substituted ester (−)-**17** as a single diastereoisomer[31] by ^{1}H NMR spectroscopy in 92% yield. A second alkylation with allyl bromide gave α,α-disubstituted (−)-**18**, again as a single diastereoisomer and in 43% yield.[31] Oxidative elimination of the methyl sulfanyl group of (−)-**18** then gave the desired α-methyl-α-allyl-substituted diene (−)-**19** in 88% yield over two steps—we chose to carry out the oxidative elimination as the final step in keeping with our earlier observation that this sequence gave the best yields of (−)-**11**.

Hexenoate-based dienes (±)-**21a** and (±)-**21b** were prepared in a manner similar to that described for (−)-**19**. Here, alkylation of (±)-**12** (prepared from racemic allyl glycine)[38] with either methyl or ethyl iodide gave the α-methyl- and α-ethyl-substituted esters (±)-**20a** and (±)-**20b**, respectively. These were then allylated to give dienes (±)-**21a** and (±)-**21b**, with the stereochemistry shown,[31] and in 47% and 42% yield, respectively. The allylation/methylation sequence was reversed to provide (±)-**22** in 68% yield via the intermediacy of (±)-**13**, thus further demonstrating the versatility of the methodology.

The thus-prepared dienes **11**, **13**, **16**, **19**, **21a**,**b**, and **22** were subjected to ring-closing metathesis (RCM) conditions in order to prepare the desired cyclic *β*-amino esters, and the results of these studies are summarized in Table 1. Initially, RCM reactions were carried out on the unsubstituted dienes **11**, **13**, and **16** using Grubbs' ruthenium catalysts **3** or **4**, in benzene at rt, and in all cases ring-closure proceeded in high yield, 92%, 91%, and 93%, respectively. It is worth noting that the diene **13** cyclized equally well in the presence of **3** at rt and at reflux to give the six-membered cyclic *β*-amino ester **24** in high yield. However, in the case of (−)-**11**, refluxing conditions gave rise to some isomerization of the double bond of the five-membered cyclic *β*-amino ester (+)-**23** to give **29** (see Figure 3)—1.5:1 by ^{1}H NMR spectroscopy.

(31) It is well documented that these conditions proceed via a doubly lithiated intermediate where alkylation of the enolate takes place with relative topicity *lk*-1, 2.[28] In all cases, we found little or no evidence of a minor isomer in the NMR spectra of crude mixtures before chromatography.

(32) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252−4259.

(33) Belokon, Y. N.; Tararov, V. I.; Maleev, V. I.; Savel'eva, T. F.; Ryzhov, M. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4249−4252.

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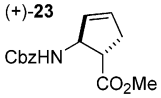
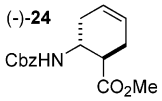
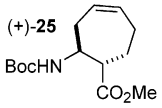
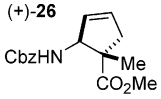
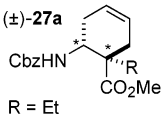
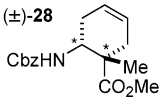
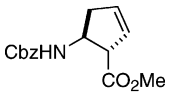
(38) Racemic material was used in this case since the reactions were done on a large scale.

TABLE 1. RCM Cyclizations

Diene	Catalyst[a] (temp)	Product	Yield[b]
(-)-**11**	**4**(rt)	(+)-**23** 	92%
	4(reflux)		89%
(+)-**13**	**3**(reflux)	(-)-**24** 	96%
(±)-**13**	**3**(rt)[c]	(±)-**24**	91%
(-)-**16**	**4**(rt)	(+)-**25** 	93%
(-)-**19**	**4**(rt)	(+)-**26** 	93%
		R = Me	
(±)-**21a**	**4**(reflux)	(±)-**27a** 	96%
		R = Et	
(±)-**21b**	**4**(reflux)	(±)-**27b**	94%
(±)-**20**	**4**(reflux)	(±)-**28** 	91%

[a] All reactions were carried out in benzene except for c, where CH_2Cl_2 was used. [b] Isolated yield after chromatography.



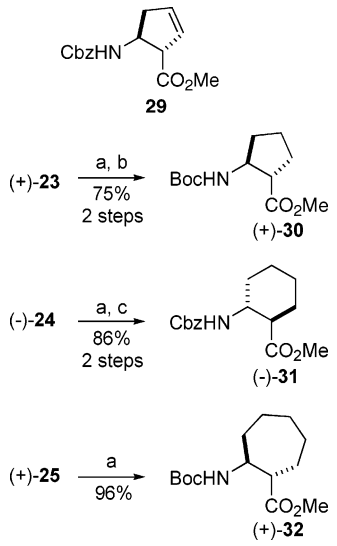
29

FIGURE 3.

Given this, we chose to treat the related, but further substituted, diene (−)-**19** with **4** at rt in order to minimize the likelihood of double-bond isomerization. This resulted in a high yield of (+)-**26** without evidence of double-bond isomerization. The substituted six-membered cyclic *β*-amino esters **27a**, **27b**, and **28** were all prepared on treatment of the respective diene with **4** at reflux, and as for diene **13**, double-bond isomerization was not observed.

Finally, the alkenes (+)-**23**, (−)-**24**, and (+)-**25** were reduced to the corresponding cycloalkanes (+)-**30**, (−)-**31**, and (+)-**32** as outlined in Scheme 4. Optical rotations obtained for aminocyclopentane carboxylic acid methyl ester (+)-**30** and aminocyclohexane carboxylic acid methyl ester (−)-**31** were in close agreement with those reported in the literature.[8,39] In addition, the 1.5:1

SCHEME 4[a]



[a] Reagents and conditions: (a) 10% Pd−carbon, H_2, MeOH, rt; (b) Boc_2O, $NaHCO_3$, MeOH, rt; (c) DIEA, CbzCl, DMAP, CH_2Cl_2, rt.

isomeric mixture of **23** and **29**, obtained previously through the cyclization of diene (−)-**11** at reflux, was reduced under the same conditions to give (+)-**30** as the sole product by ^{1}H NMR spectroscopy, further confirming our assignment of (+)-**23** and **29**. The optical rotation of this sample of (+)-**30** was also in accordance with the literature value. [39]

In conclusion, we have reported methods for the construction of methionine, allylglycine, and serine-derived dienes and their RCM conversion to 5-, 6-, and 7-membered cyclic *β*-amino esters, respectively. The R groups of methionine and serine provide a masked alkene that is liberated at the appropriate time in the synthesis. The amino acid-derived dienes cyclize equally well in refluxing benzene with either Grubbs' first- or second-generation catalysts, the exception being the 5-membered series where some doubl-bond isomerization was evident at elevated temperatures. We have also presented methods for the stereoselective introduction of a further substituent into the diene and hence the product cyclic *β*-amino esters. The double bond in the cyclic *β*-amino esters provides suitable functionality for further derivatization.[40] Finally, the double bonds of cyclic *β*-amino esters were hydrogenated to give the saturated analogues which were, in the case of **30** and **31**, identical in all respects with literature compounds.[8,39]

Experimental Section

General Method A: α-Alkylation of *β*-Amino Esters. To a suspension of anhydrous LiCl (3 equiv) in THF at −78 °C under argon was added LDA (2.2 equiv), and the solution was stirred at −78 °C for 10 min. The *N*-protected *β*-amino acid methyl ester (1 equiv) was then added, and the mixture was stirred at −78 °C for 1 h. The electrophile (4 equiv) was added slowly, and the mixture was stirred at −78 °C for 2 h and then allowed to warm to rt over 16 h. The reaction was quenched with aqueous saturated NH_4Cl, and the organic

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phase was washed with satd $NaHCO_3$ (10 mL), NH_4Cl (10 mL), and NaCl (10 mL) solutions, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel eluting with an ethyl acetate (EA)/petroleum ether (PE) mix.

General Method B: Oxidative Elimination of Methionine Side Chain. Hydrogen peroxide (1.4 equiv of 50% w/w solution) was added to a solution of the methionine derivative dissolved in acetic acid (5 mL), and the mixture was stirred at rt for 4 h. Dichloromethane (20 mL) was added, and the solution was carefully neutralized with satd aq Na_2CO_3. The organic phase was washed with water (10 mL) and dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting sulfoxide was then dissolved in degassed *m*-xylene (10 mL), sealed in a glass tube under vacuum, and heated at 200 °C for 16 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel eluting with an ethyl acetate/petroleum ether mixture.

General Method C: Synthesis of Cyclic β-Amino Acids by Ring-Closing Metathesis. A solution of catalyst **3** (or **4**) (5 mol %) in *dry degassed* benzene (or CH_2Cl_2) was added to a solution of the diene (1 equiv) in *dry degassed* benzene (or CH_2Cl_2) (∼0.1 mmol) under argon. The solution was then either stirred at rt or at reflux. The solvent was evaporated under reduced pressure, and the residue was purified by silica chromatography, eluting with an ethyl acetate/petroleum ether mix, to give the desired cyclic β-amino acid.

(3*R*)-3-Benzyloxycarbonylamino-5-methylsulfanylpentanoic Acid Methyl Ester ((−)-8). (*S*)-*N*-Cbz-methionine (5 g, 17.67 mmol) in THF (90 mL), Et_3N (2.548 mL, 17.67 mmol, 1 equiv), $ClCO_2Et$ (1.663 mL, 17.67 mmol, 1 equiv), ethereal diazomethane, and a solution of silver benzoate (445 mg, 1.94 mmol, 0.11 equiv) dissolved in Et_3N (7.128 mL, 51.24 mmol, 2.9 equiv) was reacted according to general literature procedure.[28] Purification by column chromatography (EA/PE 1:3) gave (−)-**8** (5.12 g, 93%) as a colorless oil: $[\alpha]^{20}_D = -18.8$ (*c* 1.0 $CHCl_3$); ν_{max} cm^{-1} 3321, 1736, 1690, 1541; ^1H NMR (500 MHz, $CDCl_3$) δ 1.80 (1H, m), 1.88 (1H, m), 2.09 (3H, s), 2.52 (2H, m), 2.58 (2H, m), 3.66 (3H, s), 4.09 (1H, m), 5.08 (2H, s), 5.35 (1H, d, J = 8.8 Hz), 7.32 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 30.6, 33.6, 38.5, 47.3, 51.7, 66.6, 128.0, 128.0, 128.4, 136.4, 155.7, 171.7; HRMS calcd for $C_{15}H_{22}NO_4S$ (MH^+) 312.1270, found 312.1272. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.81; H, 6.80; N, 4.50; S, 10.50. Found: C, 57.61; H, 7.04; N, 4.52; S, 10.54.

(3*S*)-3-Benzyloxycarbonylaminopentenoic Acid Methyl Ester (9). Hydrogen peroxide (0.230 mL of a 50% w/w solution, 3.25 mmol, 1.4 equiv) was reacted with (−)-**8** (720 mg, 2.32 mmol) and subjected to oxidative elimination according to general method B. Purification by radial chromatography (EA/PE 15:85) gave **9** (430 mg, 63%) as a yellow oil: ν_{max} cm^{-1} 3339, 2953, 1720.4, 1514; ^1H NMR (500 MHz, $CDCl_3$) δ 2.65 (2H, m), 3.67 (3H, s), 4.58 (1H, m), 5.11 (2H, s), 5.18 (2H, m), 5.45 (1H, brs), 5.85 (1H, m), 7.31−7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.5, 49.5, 51.3, 66.2, 67.4, 115.15, 127.6, 127.9, 128.0, 136.4, 136.5, 155.4, 171.0.

(1*S*,2*S*)-2-(1-Benzyloxycarbonylamino-3-methylsulfanylpropyl)pentanoic Acid Methyl Ester ((−)-10). Anhydrous LiCl (198 mg, 4.8 mmol, 3 equiv), LDA (1.768 mL of a 2 M solution in THF, 3.54 mmol, 2.2 equiv), and allyl bromide (0.557 mL, 6.43 mmol, 4 equiv) were reacted with (−)-**8** (500 mg, 1.61 mmol, 1 equiv) dissolved in THF (10 mL) according to general method A. Purification by radial chromatography (EA/PE 1:4) gave (−)-**10** (301 mg, 53%) as a colorless oil: $[\alpha]^{20}_D = -20.9$ (*c* 1.0 $CHCl_3$); ν_{max} cm^{-1} 3342, 2953, 1717, 1701, 1653, 1506; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (2H, m), 2.08 (3H, s), 2.31 (1H, m), 2.41 (1H, m), 2.52 (2H, m), 2.66 (1H, m), 3.67 (3H, s), 3.99 (1H, m), 5.03−5.14 (4H, m), 5.57 (1H, d, J = 9.8 Hz), 5.74 (1H, m), 7.32−7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 15.3, 30.4, 33.8, 33.8, 48.2, 50.7, 51.4, 66.4, 117.3, 127.8, 127.8, 128.2, 134.2, 136.3, 156.1, 174.3; HRMS calcd for $C_{18}H_{25}NO_4S$ (M) 351.1504, found 351.1516.

(2*S*,3*S*)-2-Allyl-3-benzyloxycarbonylamino-2-methylpent-4-enoic Acid Methyl Ester ((−)-11). (a) Hydrogen peroxide (0.086 mL of a 50% w/w solution, 1.26 mmol, 1.4 equiv) was reacted with (−)-**10** (295 mg, 0.84 mmol) and subjected to oxidative elimination according to general method B. Purification of the residue by radial chromatography (EA/PE 1:3) gave diene (−)-**11** (211 mg, 76%) as a yellow oil. (b) Anhydrous LiCl (94 mg, 2.3 mmol, 3 equiv), LDA (0.837 mL of a 2 M solution in THF, 1.67 mmol, 2.2 equiv), and allyl bromide (0.263 mL, 3.0 mmol, 4 equiv) were reacted with **9** (200 mg, 0.76 mmol, 1 equiv) dissolved in THF (4 mL) according to general method A. Purification by radial chromatography (EA/PE 15:85) gave (−)-**11** (62 mg, 27%) as a yellow oil: $[\alpha]^{20}_D = -37.1$ (*c*1.0 $CHCl_3$);. ν_{max} cm^{-1} 3342, 2953, 1724, 1643, 1504; ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (1H, m), 2.43 (1H, m), 2.72 (1H, m), 3.63 (3H, s), 4.45 (1H, m), 5.05−5.23 (6H, m), 5.76 (2H, m), 7.32−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.8, 48.6, 51.5, 53.4, 66.7, 115.8, 117.6, 127.9, 128.0, 128.4, 134.2, 136.3, 136.4, 155.9, 174.1; HRMS calcd for $C_{17}H_{21}NO_4$ (M) 303.1471, found 303.1465.

(3*R)- and (3*R*)-3-Benzyloxycarbonylaminohex-5-enoic Acid Methyl Ester (12).** (a) (±)-*N*-Cbz-allylglycine (5 g, 20.1 mmol, 1 equiv) in THF (90 mL), Et_3N (2.548 mL, 17.67 mmol, 1 equiv), $ClCO_2Et$ (1.663 mL, 17.67 mmol, 1 equiv), ethereal diazomethane, and silver benzoate (506 mg, 2.21 mmol, 0.11 equiv) dissolved in Et_3N (8.103 mL, 58.23 mmol, 2.9 equiv) was reacted according to general literature procedure.[28] Purification by column chromatography (EA/PE 1:3) gave (±)-**12** (5.254 g, 94%) as a colorless oil. (b) An equivalent reaction using (*R*)-*N*-Cbz-allylglycine (225 mg, 0.87 mmol) gave (+)-**12** (234 mg, 94%): $[\alpha]^{20}_D$ = +4.2 (*c* 2.0 $CHCl_3$, lit.[41] $[\alpha]^{20}_D = +4.7$); ν_{max} cm^{-1} 3339, 1724, 1643, 1529; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (2H, m), 2.56 (2H, brd, J = 5.4 Hz), 3.67 (3H, s), 4.06 (1H, m), 5.08 (4H, m), 5.22 (1H, m), 5.74 (1H, m), 7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 38.6, 47.5, 51.6, 66.5, 118.4, 127.9, 128.0, 128.4, 133.7, 136.4, 155.6, 171.8; HRMS calcd for $C_{15}H_{19}NO_4$ (MH^+) 278.1392, found 278.1391. Anal. Calcd for $C_{15}H_{19}NO_4$. C, 64.96; H, 6.91; N, 5.05. Found: C, 64.67; H, 6.79; N, 5.33.

(2*R,3*R**)- and (2*R*,3*R*)-2-Allyl-3-benzyloxycarbonylaminohex-5-enoic Acid Methyl Ester (13).** (a) Anhydrous LiCl (294 mg, 7.17 mmol, 3 equiv), LDA (2.629 mL of a 2 M solution in THF, 5.25 mmol, 2.2 equiv), and allyl bromide (0.833 mL, 9.56 mmol, 4 equiv) were reacted with (+)-**12** (662 mg, 2.39 mmol, 1 equiv), dissolved in THF (12 mL) according to general method A. Purification by radial chromatography (EA/PE 1:4) gave (+)-**13** (370 mg, 49%) as a colorless oil: $[\alpha]^{20}_D = +8.3$ (*c*1.0 CH_2Cl_2). (b) An equivalent reaction using (±)-**12** (1 g) gave (±)-**13** (672 mg, 59%): ν_{max} cm^{-1} 3344, 2953, 1717, 1643, 1506; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18−2.44 (4H, m), 2.69 (1H, m), 3.67 (3H, s), 3.93 (1H, m), 5.02−5.13 (6H, m), 5.63 (1H, d, J = 9.8 Hz), 5.73 (2H, m), 7.35 (5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 39.0, 47.5, 51.2, 51.6, 66.6, 117.5, 118.1, 127.9, 128.0, 128.4, 133.8, 134.4, 136.6, 156.1, 174.7; HRMS calcd for $C_{18}H_{23}NO_4Na$ (MNa^+) 340.1525, found 340.1536. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.3; N, 4.41. Found: C, 68.37; H, 7.47; N, 4.53.

(3*S*)-3-*tert*-Butoxycarbonylaminohept-6-enoic Acid Methyl Ester ((−)-15). To a solution of (−)-**14**[36] (1.37 g, 5.63 mmol, 1 equiv) dissolved in MeOH (∼0.05 M) was added 1 M aq NaOH (11.3 mL of 2 M solution, 11.3 mmol, 2 equiv) and the solution stirred at reflux for 4 h. The MeOH was removed under reduced pressure, and water was added to make a workable volume. The solution was acidified to pH 2 with 10% HCl and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the free acid (1.29 g, quant). The free acid (1.29 g, 5.63 mmol, 1 equiv) in THF (20 mL) was treated with Et_3N (0.784 mL, 5.63

(41) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231−234.

mmol, 1 equiv), $ClCO_2Et$ (0.536 mL, 5.63 mmol, 1 equiv), ethereal diazomethane, and silver benzoate (159 mg, 0.11 equiv) dissolved in Et_3N (2.535 mL, 16.3 mmol, 2.9 equiv) according to the general literature procedure.[28] Purification by column chromatography (EA/PE 1:9−1:3) gave (−)-**15** (1.382 g, 96%) as a colorless oil: $[\alpha]^{20}_D = -10$ (*c*1.06 CH_2Cl_2) [lit. (ent)[37] $[\alpha]^{20}_D = +20.8$)]; ν_{max} cm^{-1} 3361, 2978, 1734, 1710, 1517, 1367, 1170; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.60 (2H, m), 2.10 (2H, m), 2.52 (2H, m), 3.68 (3H, s), 3.92 (1H, m), 4.93 (1H, d, $J = 8.3$ Hz), 4.96−5.05 (2H, m), 5.79 (1H, m); ^{13}C (75 MHz, $CDCl_3$) δ 28.3, 30.3, 33.7, 39.0, 47.1, 51.6, 79.2, 115.2, 137.6, 155.3, 172.1; HRMS calcd for $C_{15}H_{19}NO_4$ (MNa^+) 280.1525, found 280.1529.

(3*S*)-2-Allyl-3-*tert*-butoxycarbonylaminohept-6-enoic Acid Methyl Ester [(−)-16]. Anhydrous LiCl (73 mg, 1.75 mmol, 3 equiv), LDA (0.642 mL of a 2 M solution in THF, 1.28 mmol, 2.2 equiv), and allyl bromide (0.202 mL, 9.56 mmol, 4 equiv) were reacted with (−)-**15** (150 mg, 0.58 mmol, 1 equiv) dissolved in THF (3 mL) according to general method A. Purification by radial chromatography (EA/PE 1:20) gave (−)-**16** (71 mg, 42%) as a colorless oil: $[\alpha]^{20}_D = -23$ (*c*1.0 $CHCl_3$); ν_{max} cm^{-1} 2930, 1717, 1507, 1367, 1169; ^1H NMR δ 1.43 (9H, s), 1.47 (2H, m), 2.10 (2H, dd, $J = 15.1$ and 6.8 Hz), 2.31 (1H, m), 2.40 (1H, m), 2.62 (1H, m), 3.68 (3H, s), 3.81 (1H, m), 4.54−5.09 (4H, m), 5.22 (1H, d, $J = 10.3$ Hz), 5.72−5.81 (2H, m); ^{13}C NMR δ 28.3, 30.4, 33.9, 34.1, 48.6, 50.4, 51.5, 79.0. 115.1, 117.3, 134.7, 137.7, 155.7, 174.9; HRMS calcd for $C_{16}H_{27}NO_4$-Na (MNa^+) 320.1838, found 320.1835.

(2*S*,3*S*)-3-Benzyloxycarbonylamino-2-methyl-5-methylsulfanylpentanoic Acid Methyl Ester ((−)-17). Anhydrous LiCl (396 mg, 9.65 mmol, 3 equiv), LDA (3.537 mL of a 2 M solution in THF, 7.07 mmol, 2.2 equiv), and MeI (0.801 mL, 12.86 mmol, 4 equiv) were reacted with (−)-**8** (1 g, 3.22 mmol), dissolved in THF (15 mL), according to general method A. Purification by radial chromatography (EA/PE 1:4) gave (−)-**17** (0.962 g (92%) as a colorless oil: $[\alpha]^{20}_D = -14.3$ (*c*1.0 $CHCl_3$); ν_{max} cm^{-1} 3337, 2953, 1717, 1699, 1510, 1454; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, d, $J = 6.8$ Hz), 1.73 (2H, m), 2.08 (3H, s), 2.52 (2H, m), 2.70 (1H, m), 3.67 (3H, s), 3.91 (1H, m), 5.10 (2H, dd, $J = 12.4$ and 14.4 Hz), 5.49 (1H, d, $J = 9.8$ Hz), 7.29−7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.8, 15.5, 30.7, 33.6, 42.6, 51.7, 52.6, 66.6, 127.9, 128.0, 128.4, 136.5, 156.5, 175.4; HRMS calcd for $C_{16}H_{24}NO_4S$ (MH^+) 326.1426, found 326.1429. Anal. Calcd: C, 59.05; H, 7.12; N, 4.30; S, 9.85. Found: C, 59.15; H, 7.30; N, 4.40; S, 9.95.

(1*S*,2*S*)-2-(1-Benzyloxycarbonyl-3-methylsulfanylpropyl)-2-methylpent-3-enoic Acid Methyl Ester ((−)-18). Anhydrous LiCl (326 mg, 7.95 mmol, 3 equiv), LDA (2.918 mL of a 2 M solution in THF, 5.83 mmol, 2.2 equiv), and allyl bromide (0.918 mL, 10.6 mmol, 4 equiv) were reacted with (−)-**17** (862 mg, 2.65 mmol), dissolved in THF (15 mL), according to general method A. Purification by radial chromatography (EA/PE 1:9) gave (−)-**18** (411 mg, 43%) as a colorless oil: $[\alpha]_D = -30.6$ (*c*1.0 $CHCl_3$); ν_{max} cm^{-1} 3343, 2951, 1720, 1641, 1510; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.42 (1H, m), 1.91 (1H, m), 2.07 (3H, s), 2.23 (1H, dd, $J = 7.4$ and 13.7 Hz) 2.43−2.58 (3H, m), 3.66 (3H, s), 3.79 (1H, dt, $J = 10.7$ and 2.4 Hz), 5.02−5.16 (4H, m), 5.42 (1H, d, $J = 10.7$ Hz), 5.67 (1H, m), 7.31−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 19.5, 31.2, 31.4, 41.2, 49.8, 51.8, 56.3, 66.7, 118.9, 128.0, 128.1, 128.4, 132.9, 136.5, 156.4, 175.8.

(2*S*,3*S*)-2-Allyl-3-benzyloxycarbonylamino-2-methylpent-4-enoic Acid Methyl Ester ((−)-19). Hydrogen peroxide (0.092 mL of a 50% w/w solution, 1.35 mmol, 1.4 equiv) was reacted with (−)-**18** (352 mg, 0.97 mmol) and subjected to oxidative elimination according to general method B. Purification of the residue by radial chromatography (EA/PE 1:3) gave diene (−)-**19** (267 mg, 88%) as a colorless oil: $[\alpha]^{20}_D = -30.2$ (*c*1.0 $CHCl_3$); ν_{max} cm^{-1} 3342, 2951, 1707, 1641, 1501; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s), 2.26 (1H, dd, $J = 7.3$ and 13.7 Hz), 2.51 (1H, dd, $J = 7.3$ and 13.7 Hz), 3.65 (3H, s), 4.22 (1H, t, $J = 8.3$ Hz), 5.04−5.26 (6H, m), 5.71 (2H, m), 7.26−7.36 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 41.0, 49.3, 51.8, 59.2, 66.7, 117.83, 119.0, 128.1, 128.4, 132.7, 134.3, 136.4, 155.7, 175.6; HRMS calcd for $C_{18}H_{23}NO_4Na$ (MNa^+) 340.1525, found 340.1526.

(2*R,3*R**)-2-Methyl-3-benzyloxycarbonylaminohex-5-enoic Acid Methyl Ester ((±)-20a).** Anhydrous LiCl (266 mg, 6.5 mmol, 3 equiv), LDA (2.383 mL of a 2 M solution in THF, 4.76 mmol, 2.2 equiv), and MeI (0.543 mL, 8.66 mmol, 4 equiv) were reacted with (±)-**12** (600 mg, 2.17 mmol) dissolved in THF (10 mL), according to general method A. Purification by radial chromatography (EA/PE 1:4) gave (±)-**20a** (543 mg, 86%) as a colorless oil: ν_{max} cm^{-1} 3317, 2952, 1717, 1642, 1506, 1206; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, d, $J = 6.$Hz), 2.26 (2H, m), 2.73 (1H, m), 3.67 (3H, s), 3.86 (1H, m), 5.08 (4H, m), 5.50 (1H, d, $J = 9.3$ Hz), 5.75 (1H, m), 7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 38.2, 41.7, 51.5, 52.8, 66.4, 117.8, 127.8, 127.9, 128.3, 133.9, 136.5, 156.2, 175.4. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.05; H, 7.33; N, 4.99.

(2*R,3*R**)-3-Benzyloxycarbonylamino-2-ethylhex-5-enoic Acid Methyl Ester ((±)-20b).** Anhydrous LiCl (193 mg, 4.7 mmol, 3 equiv), LDA (1.727 mL of a 2 M solution in THF, 3.45 mmol, 2.2 equiv), and EtI (0.503 mL, 6.28 mmol, 4 equiv) were reacted with (±)-**12** (435 mg, 1.57 mmol) dissolved in THF (10 mL), according to general method A. Purification by radial chromatography (EA/PE 15/85) gave (±)-**20b** (302 mg, 63%) as a colorless oil: ν_{max} cm^{-1} 3342, 2930, 1720, 1643, 1502, 1227; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ Hz), 1.58 (1H, m), 1.71 (1H, m), 2.17−2.27 (2H, m), 2.51 (1H, m), 3.68 (3H, s), 3.93 (1H, m), 5.05−5.13 (4H, m), 5.62 (1H, d, $J = 9.8$ Hz), 5.75 (1H, m), 7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 23.0, 38.7, 49.2, 51.0, 51.3, 66.3, 117.8, 127.7, 127.8, 128.2, 133.8, 136.5, 156.1, 175.2; HRMS calcd for $C_{17}H_{24}NO_4$ (MH^+) 306.1705, found 306.1711. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.14; H, 7.31; N, 4.59.

(2*R,3*R**)-2-Allyl-3-benzyloxycarbonylamino-2-methylhex-5-enoic Acid Methyl Ester ((±)-21a).** Anhydrous LiCl (25 mg, 0.62 mmol, 3 equiv), LDA (0.226 mL of a 2 M solution in THF, 0.45 mmol, 2.2 equiv), and allyl bromide (0.072 mL, 0.84 mmol, 4 equiv) were reacted with (±)-**20a** (60 mg, 0.21 mmol) dissolved in THF (1 mL), according to general method A. Purification by radial chromatography (EA/PE 1:9) gave (±)-**21a** (32 mg, 47%) as a colorless oil: ν_{max} cm^{-1} 3348, 3076, 2980, 1724, 1641; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.93 (1H, m), 2.24 (1H, dd, $J = 7.3$ and 13.7 Hz), 2.43 (1H, m), 2.51 (1H, dd, $J = 7.3$ and 13.7 Hz), 3.65 (3H, s), 3.80 (1H, td, $J = 3.4$ and 10.8 Hz), 5.07 (6H, m), 5.44 (1H, d, $J = 10.7$ Hz), 5.79 (2H, m), 7.30 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 36.0, 41.3, 49.6, 51.7, 56.3, 66.5, 117.5, 118.8, 127.9, 127.9, 128.4, 133.0, 134.4, 136.6, 156.2, 175.9; HRMS calcd for $C_{19}H_{25}NO_4$ (MH^+) 332.1862, found 332.1863. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.80; H, 7.60; N, 4.23.

(2*R,3*R**)-2-Allyl-3-benzyloxycarbonylamino-2-ethylhex-5-enoic Acid Methyl Ester ((±)-21b).** Anhydrous LiCl (36 mg, 0.89 mmol, 3 equiv), LDA (0.324 mL of a 2 M solution in THF, 0.65 mmol, 2.2 equiv), and allyl bromide (0.103 mL, 1.2 mmol, 4 equiv) were reacted with (±)-**20b** (90 mg, 0.3 mmol) dissolved in THF (1.5 mL), according to general method A. Purification by radial chromatography (EA/PE 1:9) gave (±)-**21b** (41 mg, 42%) as a colorless oil: ν_{max} cm^{-1} 3350, 2930, 1720, 1643, 1502, 1223; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 7.5$ Hz), 1.64 (1H, m), 1.78−1.96 (2H, m), 2.35 (2H, m), 2.52 (1H, ddd, $J = 6.8$, 16.1, and 30.7 Hz), 3.68 (3H, s), 3.97 (1H, ddd, $J = 3.2$, 11.3, and 21.2 Hz), 4.97−5.14 (6H, m), 5.32 (1H, d, $J = 10.3$ Hz), 5.55−5.77 (2H, m), 7.35 (5H, m); ^{13}C NMR ($CDCl_3$) δ 7.7, 24.3, 36.2, 36.3, 51.8, 52.9, 54.1, 66.6, 117.4, 118.3, 127.9, 128.0, 128.4, 133.7, 134.5, 136.7, 156.5, 175.8.

(2*S,3*R**)-2-Allyl-3-benzyloxycarbonylamino-2-methylhex-5-enoic Acid Methyl Ester ((±)-22).** Anhydrous LiCl (43 mg, 1.0 mmol, 3 equiv), LDA (0.381 mL of a 2 M solution in THF, 0.76 mmol, 2.2 equiv), and MeI (0.086 mL, 1.4 mmol, 4 equiv) were reacted with (±)-**13** (110 mg, 0.35 mmol)

dissolved in THF (1.8 mL), according to general method A. Purification by radial chromatography (EA/PE 15:85) gave (±)-**22** (71 mg, 68%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s), 1.99 (1H, m), 2.19−2.33 (2H, m), 2.56 (1H, dd, J = 6.6 and 23.9 Hz), 3.67 (3H, s), 4.00 (1H, td, J = 3.4 and 10.7 Hz), 4.93 (1H, d, J = 10.3 Hz), 4.97−5.13 (6H, m), 5.73 (2H, m), 7.29−7.37 (5H, m).

(2*S*,3*S*)-*3*-Benzyloxycarbonylaminocyclopent-3-enecarboxylic Acid Methyl Ester (+)-23 and (1*S*,5*S*)-*5*-Benzyloxycarbonylaminocyclopenten-2-enecarboxylic Acid Methyl Ester 29. (a) A solution of **4** (18 mg, 5 mol %), in benzene (0.5 mL), was added to a solution of diene (−)-**11** (126 mg, 0.42 mmol, 1 equiv), in benzene (4 mL), and the solution stirred at rt for 2 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (+)-**23** (105 mg, 92%) as a white solid. (b) In a second reaction, a solution of **4** (4.2 mg, 5mol %), in benzene (0.5 mL), was added to a solution of diene (−)-**11** (30 mg, 0.1 mmol, 1 equiv), in benzene (1 mL), and stirred at reflux for 4 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave a fraction containing **23** and **29** (24 mg, 89%), in a ratio of 1.5:1 by ^{1}H NMR, that could not be separated further. Data for (+)-**23**: $[\alpha]^{20}_D$ = +102.3 (*c*1.0 $CHCl_3$); mp 92−93 °C; ν_{max} cm^{-1} 2953, 1734, 1684, 1537; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (1H, m), 2.75 (1H, m), 2.87 (1H, m), 3.72 (3H, s), 4.86 (1H, brs), 5.06 (1H, m), 5.12 (2H, m), 5.63 (1H, brs), 5.86 (1H, m), 7.30−7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 35.5, 50.7, 52.1, 61.1, 66.7, 128.1, 128.5, 130.0, 132.4, 133.5, 136.3, 155.5, 174.8; HRMS Calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1158. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.23; N, 5.09. Found: C, 65.13; H, 6.31; N, 5.25. Selected data for **29** (from mixture): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (1H, brd, J = 17.6 Hz), 2.93 (1H, dd, J = 7.3 and 17.1 Hz), 3.28 (1H, brs), 4.58 (1H, m), 4.83 (1H, brs), 5.69 (1H, s), 5.86 (1H, s).

(1*R,2*R**)- and (1*R*,2*R*)-*2*-Benzyloxycarbonylaminocyclohex-4-enecarboxylic Acid Methyl Ester (24).** (a) A solution of **3** (7 mg, 5mol %) in CH_2Cl_2 (0.5 mL) was added to a solution of (±)-**13** (54 mg, 0.17 mmol), in CH_2Cl_2 (1 mL), and stirred at rt for 2 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (±)-**24** (49 mg, 91%) as a colorless oil. (b) A solution of **3** (8 mg, 0.01 mmol, 5mol %), in benzene (0.5 mL), was added to a solution of diene (+)-**13** (59 mg, 0.19 mmol), in benzene (10 mL), and stirred at reflux for 4 h according to general method C to give (−)-**24** (51 mg, 96%): $[\alpha]^{20}_D$ = −31.2 (*c* 1 $CHCl_3$) (lit.[19] $[\alpha]^{20}_D$ = 33.5); ν_{max} cm^{-1} 3339, 3032, 2930, 2853, 1732, 1520; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (1H, brd, J = 9.8 Hz), 2.30 (1H, dd, J = 12.2 and 5.9 Hz), 2.49 (2H, m), 2.72 (1H, m), 3.64 (3H, s), 4.11 (1H, m), 4.90 (1H, brs), 5.08 (2H, s), 5.59 (1H, m), 5.66 (1H, m), 7.33 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 31.0, 44.3, 47.8, 51.8, 66.6, 124.1, 124.9, 128.0, 128.1, 128.4, 136.4, 155.5, 173.9; HRMS calcd for $C_{16}H_{20}NO_4$ (MH^+) 290.1392, found 290.1402. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.48; H, 6.62; N, 4.84. Found: C, 66.38; H, 6.83; N, 4.94.

(1*S*,2*S*)-2-*tert*-Butoxycarbonylaminocyclohept-4-enecarboxylic Acid Methyl Ester ((+)-25). A solution of catalyst **4** (6 mg, 5 mol %), in benzene (0.5 mL), was added to a solution of diene (−)-**16** (40 mg, 0.13 mmol), in benzene (3 mL), and stirred at rt for 2 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (+)-**18** (33 mg, 93%) as a white solid: $[\alpha]^{20}_D$ = +2 (*c*1.0, $CHCl_3$); mp 72−74 °C; ν_{max} cm^{-1} 3371, 2936, 1736, 1686, 1524; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.45 (1H, m), 2.02 (1H, m), 2.08−2.21 (2H, m), 2.28 (1H, dd, J = 7.1 and 13.7 Hz), 2.40 (1H, m), 2.43 (1H, m), 3.67 (3H, s), 4.05 (1H, m), 4.63 (1H, brs), 5.73 (1H, m), 5.83 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 27.3, 28.3, 32.3, 49.7, 51.8, 54.1, 79.3, 128.8, 133.0, 154.6, 174.3; HRMS calcd for $C_{14}H_{23}NO_4Na$ (MNa^+) 292.1525, found 292.1526.

(1*S*,2*S*)-2-Benzyloxycarbonylamino-1-methylcyclopen-3-enecarboxylic Acid Methyl Ester ((+)-26). A solution of catalyst **4** (24 mg, 5mol %), in benzene (0.5 mL), was added to a solution of diene (−)-**19** (180 mg, 0.57 mmol), in benzene (5 mL), and stirred at rt for 2 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (+)-**26** (151 mg, 92%) as a white solid: $[\alpha]^{20}_D$ = +50.5 (*c*1.0 $CHCl_3$); ν_{max} cm^{-1} 3350, 2951, 1697, 1634, 1502; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, s), 2.24 (1H, d, J = 17.1 Hz), 2.95 (1H, d, J = 17.1 Hz), 3.73 (3H, s), 4.74 (1H, brd, J = 7.3 Hz), 5.10 (2H, dd_{AB}, J = 12.5 Hz), 5.21 (1H, brd, J = 9.3 Hz), 5.53 (1H, brs), 5.83 (1H, brs), 7.25−7.36 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 44.2, 51.4, 52.1, 62.8, 66.5, 127.9, 128.3, 129.5, 131.6, 131.8, 136.4, 155.7, 177.2; HRMS calcd for $C_{16}H_{19}NO_4$ (MH^+) 290.1392), found 290.1396.

(1*R,2*R**)-2-Benzyloxycarbonylamino-1-methylcyclohex-4-enecarboxylic Acid Methyl Ester ((±)-27a).** A solution of catalyst **4** (3 mg, 5mol %), in benzene (0.5 mL), was added to a solution of diene (±)-**21a** (25 mg, 0.08 mmol), in benzene (1 mL), and stirred at reflux for 4 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (±)-**27a** (24 mg, 96%) as a colorless oil: ν_{max} cm^{-1} 3346, 3032, 2932, 2851, 1728, 1526; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.89 (1H, dd, J = 17.1 and 2 Hz), 1.95 (1H, dd, J = 17.6 and 2 Hz), 2.42 (1H, d, J = 17.6 Hz), 2.72 (1H, d, J = 17.1), 3.65 (3H, s), 4.31 (1H, m), 4.79 (1H, d, J = 9.3 Hz), 5.09 (2H, s), 5.56 (1H, m), 5.65 (1H, m), 7.35 (5H, m).

(1*R,2*R**)-2-Benzyloxycarbonylamino-1-ethylcyclohex-4-enoic Acid Methyl Ester ((±)-27b).** A solution of catalyst **4** (2.5 mg, 5mol %), in benzene (0.5 mL), was added to a solution of diene (±)-**21b** (21 mg, 0.06 mmol), in benzene (1 mL), and stirred at reflux for 4 h according to general method C. Purification by radial chromatography (EA/PE 1:9) gave (±)-**27b** (18 mg, 94%) as a colorless oil: ν_{max} cm^{-1} 3343, 3032, 2951, 1732, 1717, 1504, 1454, 1234; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (1H, t, J = 7.8 Hz), 1.51 (1H, ddd, J = 28.8, 14.2, and 7.3 Hz), 1.77 (2H, m), 2.02 (1H, d, J = 18.6 Hz), 2.38 (1H, d, J = 18.6 Hz, 1H), 2.75 (1H, d, J = 18.6 Hz), 3.68 (3H, s), 4.37 (1H, d, J = 10.2 Hz), 4.86 (1H, d, J = 10.2 Hz), 5.10 (2H, dd, J = 21.5 and 2.2 Hz), 5.55 (1H, m), 5.70 (1H, m), 7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 28.6, 29.3, 30.5, 49.0, 49.8, 51.9, 66.9, 123.4, 125.9, 128.2, 128.5, 136.3, 156.3, 175.0; HRMS calcd for $C_{18}H_{24}NO_4$ (MH^+) 318.1705, found 318.1691.

(1*S,2*R**)-2-Benzyloxycarbonylamino-1-methylcyclohex-4-enecarboxylic Acid Methyl Ester ((±)-28).** A solution of catalyst **4** (1.7 mg, 5mol %), in benzene (0.5 mL), was added to a solution of diene (±)-**20** (14 mg, 0.04 mmol, 1 equiv), in benzene (1 mL), and stirred at reflux for 4 h according to general method C. Purification by radial chromatography (EA/PE 1:3) gave (±)-**28** (12 mg, 91%) as a colorless oil: ν_{max} cm^{-1} 3437, 2951, 1724, 1504; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, s), 2.06 (1H, dd, J = 2.4 and 21.0 Hz), 2.12 (1H, m), 2.37 (1H, m), 2.69 (1H, dd, J = 4.4 and 17.1 Hz), 3.66 (3H, s), 3.94 (1H, m), 5.10 (2H, dd, J = 1.0 and 12.7 Hz), 5.56−5.65 (3H, m), 7.30.7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 30.8, 35.1, 45.2, 51.9, 52.6, 66.6, 125.1, 125.3, 128.0, 128.5, 136.6, 156.2, 176.6; HRMS calcd for $C_{17}H_{21}NO_4$ (MH^+) 303.1475, found 303.1471.

(1*S*,2*S*)-2-*tert*-Butyloxycarbonylaminocyclopentanecarboxylic Acid Methyl Ester ((+)-30). To a solution of (+)-**23** (30 mg, 0.11 mmol), dissolved in dry MeOH (3 mL) under a hydrogen atmosphere, was added 10% palladium-on-carbon (6 mg, 20% w/w). The solution was then deoxygenated and stirred vigorously under hydrogen for 12 h. The mixture was filtered through a small bed of Celite and washed with MeOH, and the solvent volume was reduced to approximately 2 mL. $NaHCO_3$ (14 mg, 0.17 mmol, 1.5 equiv) and di-*tert*-butyl dicarbonate (37 mg, 0.17 mmol, 1.5 equiv) was then added and the solution stirred at rt for 3 h. Removal of the solvent under reduced pressure and purification of the residue by radial chromatography (EA/PE 1:7) gave (+)-**30** (20 mg, 75%) as a white solid: $[\alpha]^{20}_D$ = +41.6 (*c* 0.65 $CHCl_3$) [lit.[39] $[\alpha]^{20}_D$ = +44.6 (*c* 1.3)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.47 (1H,

m) 1.72 (2H, m), 1.89 (1H, m), 1.97 (1H, m), 2.11 (1H, m), 2.57 (1H, dd, J = 16.1 and 8.3 Hz), 3.68 (3H, s), 4.11 (1H, m), 4.57 (1H, brs).

(1*R*,2*R*)-2-Benzyloxycarbonylaminocyclohexanecarboxylic Acid Methyl Ester ((−)-31). To a solution of (−)-**17** (50 mg, 0.17 mmol, 1 equiv) dissolved in MeOH (3 mL) was added 10% palladium-on-carbon (10 mg, 20% w/w). The solution was then deoxygenated and stirred vigorously under hydrogen for 12 h. The mixture was filtered through Celite, washing with MeOH, and the solvent removed under reduced pressure. The residue was then taken up in CH_2Cl_2 (3 mL) and diisopropylethylamine (0.072 mL, 0.42 mmol, 2.4 equiv), benzylchloroformate (0.04 mL, 0.27 mmol, 1.6 equiv) and (dimethylamino)pyridine (6.2 mg, 0.05 mmol, 0.3 equiv) were added, and the solution was stirred at rt overnight. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate, successively washed with satd aq $NaHCO_3$ (10 mL), NaCl (10 mL), and water (10 mL), and dried ($MgSO_4$) and the solvent removed to give (−)-**31** (43 mg, 86%) as a colorless oil: $[\alpha]^{20}_D = -18.4$ (c 0.9 $CHCl_3$ (lit.[8] $[\alpha]^{20}_D = -18$); ν_{max} cm^{-1} 3331, 1733; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13−1.44 (3H, m), 1.56−1.81 (3H, m), 1.90 (1H, m), 2.06 (1H, m), 2.27 (1H, m), 3.61 (3H, s), 3.73 (1H, ddd, J = 20.5,11.3, and 4.2 Hz), 4.08 (1H, brs), 5.06 (2H, s), 7.27−7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 24.6, 28.6, 32.8, 49.7, 51.7, 66.5, 128.0, 128.4, 136.6, 155.4, 174.3; HRMS calcd for $C_{16}H_{21}NO_4$ (M^+) 291.1471, found 291.1474.

(1*S*,2*S*)-2-*tert*-Butoxycarbonylaminocycloheptanecarboxylic Acid Methyl Ester ((+)-32). To a solution of (+)-**25** (15 mg, mmol, 1 equiv) dissolved in dry MeOH (∼0.05 M) was added 10% palladium-on-carbon (5 mg). The solution was then deoxygenated and stirred vigorously under hydrogen for 12 h. The mixture was then filtered through a small bed of Celite and washed with MeOH and the solvent removed under reduced pressure to give (+)-**32** (15 mg, 96%) as a white solid: $[\alpha]^{20}_D = +2$ (c 0.5 $CHCl_3$); ν_{max} cm^{-1} 3364, 2936, 1730, 1686, 1524; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.40−1.92 (10H, m), 2.43 (1H, m), 3.66 (3H, s), 3.91 (1H, m), 4.57 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 26.0, 28.0, 28.3, 34.4, 51.8, 52.2, 53.5, 154.8, 175.5; HRMS calcd for $C_{14}H_{25}NO_4Na$ (MNa^+) 294.1681, found 294.1678.

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Supporting Information Available: NMR spectra of compounds (−)-**8**, **9**, (−)-**10**, (−)-**11**, (+)-**12**, (+)-**13**, (−)-**15**, (−)-**16**, (−)-**17**, (−)-**18**, (−)-**19**, **20a**,**b**, **21a**,**b**, **22**, (+)-**23**, **24**, (+)-**25**, (+)-**26**, **27a**,**b**, **28**, (+)-**30**, (−)-**31**, and (+)-**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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