# Asymmetric Eschenmoser-Claisen Rearrangement for Anti-β-

# Substituted $\gamma$ , $\delta$ -Unsaturated Amino Acids

Hongchang Qu, Xuyuan Gu, Zhihua Liu, Byoung J. Min, Victor J. Hruby

Department of Chemistry, University of Arizona, 1306 E. University Boulevard,

### Tucson, AZ 85721, U. S. A.

Email: hruby@u.arizona.edu

#### **General Information**

All starting materials and reagents were purchased from Sigma-Aldrich and used without further purification. THF was distilled over sodium and benzophenone. Methylene chloride was distilled over CaH<sub>2</sub>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker DRX500 (500 MHz and 125 MHz, respectively) or Varian Inova 600 (600 MHz and 150 MHz, respectively) spectrometers with CDCl<sub>3</sub> or TMS as internal standard. Coupling constants, *J*, are reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. IR spectra were recorded on a Nicolet Impact 410 IR spectrometer. HPLC was performed on a HP 1100 liquid chromatograph using a Chiralpak AD RH column (150 × 4.6 mm). Mass spectra were obtained from Mass Spectrometry Facility, Department of Chemistry, University of Arizona. Flash column chromatography was performed using silica gel 60 from the EM Science. TLC plates (Silica Gel 60  $F_{254}$ ) were purchased from the EMD Chemicals and were visualized by UV and KMnO<sub>4</sub> stain. All new compounds were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and HRMS.



### Benzyl 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-oxoethylcarbamate (2).

N<sup>α</sup>-Cbz-Glycine (791 mg, 3.78 mmol), HOAT (514 mg, 3.78 mmol) were dissolved in dry DCM (20.0 mL) in a 50-mL flask under argon atmosphere. To the solution was added DIC (592  $\mu$ L, 3.78 mmol) and the mixture was stirred for 15 min at room temperature before (2R,5R)-dimethyl pyrrolidine (400  $\mu$ L, 3.44 mmol) was added. The stirring was continued for 24 h. Then the mixture was filtered to remove the precipitate formed, and the filtrate was concentrated to give the crude product, which was purified by flash column chromatography (Hexane:EtOAc = 3:1–2:1) to give **2** as a colorless oil (933 mg, 93.4%).  $R_f = 0.33$  (Hexane:EtOAc = 1:1),  $[\alpha]^{23.6}_{D}$  –40.6 (*c* 2.20, MeOH), HRMS (EI) calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 290.1630, found 290.1643. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.19 (t, 6H, *J* = 5.2 Hz), 1.55 (dd, 1H, *J* = 5.7, 11.9 Hz), 1.65 (dd, 1H, *J* = 5.7, 11.9 Hz), 2.16 (m, 2H), 3.89–4.08 (m, 3H), 4.22 (m, 1H), 5.12 (s, 2H), 5.77 (s, 1H), 7.28–7.45 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>) δ 18.88, 21.17, 28.76, 30.81, 43.40, 52.91, 53.60, 66.65, 127.83, 127.87, 128.32, 136.41, 156.13, 166.20. IR (NaCl): 3409.5, 3300.1, 2967.7, 1716.7, 1637.9, 1432.3, 1248.6, 1043.0.

General procedure for the preparation of compounds 5. To a 25-mL flask was added compound 2 (1.0 mmol), 2,6-di-tert-butylpyridine (1.0 mmol), and MeOTf (2.2 mmol) at ambient temperature. The mixture was stirred under argon atmosphere for 4 h before dry DCM (2 mL) was added to dissolve the salt formed. The solution was then cooled to -35 °C and was ready to react with a pre-generated lithium allylic oxide (4.0 mmol) in dry DCM (or dry toluene for 5b and 5c). The lithium allylic oxide in DCM or toluene was prepared in advance by dissolving an allylic alcohol (4.0 mmol) in dry DCM or toluene (10 mL) followed by the addition of n-butyl lithium (4.0 mmol) at -35 °C. After 15 min at this temperature, the solution was cannulated into the above Meerwein salt solution and the resultant mixture was warmed up to ambient temperature (or 60 °C for **5b** and **5c**) over a period of 4 h. Then the reaction was quenched by the addition of a saturated ammonium chloride solution (5 mL). The organic layer was separated and washed with a saturated ammonium chloride solution (5 mL  $\times$  2) and dried over MgSO<sub>4</sub>. The dry solution was concentrated under reduced pressure, and the crude product was purified by flash column chromatography to afford compounds 5. Note: in the case of 5c, the Meerwein salt solution in DCM was added to the lithium allylic oxide solution in toluene that was too viscous to be cannulated.



### Benzyl-(R)-1-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-oxopent-4-en-2-

**ylcarbamate** (**5a**). Compound **2** (292 mg, 1.00 mmol), 2,6-di-*tert*-butylpyridine (224  $\mu$ L, 1.00 mmol), MeOTf (243  $\mu$ L, 2.21 mmol), allyl alcohol (272  $\mu$ L, 4.00 mmol), nbutyl lithium (1.46 M in hexane, 2.74 mL, 4.00 mmol). Product **5a**: colorless oil, 248 mg, yield 75.2%,  $R_f = 0.55$  (Hexane:EtOAc = 1:1), HRMS (FAB) calcd for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub> (MH<sup>+</sup>) 331.2022, found 331.2040. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.13 (d, 3H, J = 6.3 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.52 (dd, 1H, J = 6.3, 12.2 Hz), 1.57 (dd, 1H, J = 6.3, 12.2 Hz), 2.07 (m, 1H), 2.21 (m, 1H), 2.43 (m, 2H), 4.15 (m, 1H), 4.36 (m, 1H), 4.47 (m, 1H), 5.02–5.15 (m, 4H), 5.29 (d, 1H, J = 9.6 Hz), 5.77 (m, 1H), 7.26–7.36 (m, 5H); <sup>13</sup>C (150 MHz, CDCl<sub>3</sub>) δ 18.38, 22.76, 28.97, 30.71, 37.07, 51.86, 53.44, 53.76, 66.66, 118.40, 127.68, 127.90, 128.34, 133.13, 136.30, 156.00, 170.31. IR (NaCl): 3269.5, 2967.7, 1712.3, 1624.8, 1537.3, 1436.7, 1253.0. HPLC analysis: de>88.2% Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O: 65/35, 0.5

HPLC analysis: de>88.2% Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O: 65/35, 0.5 mL/min, 254 nm); retention times of the diastereomeric mixture: 11.7 min and 15.8 min (**5a**).



Benzyl (*R*)-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-3,3-dimethyl-1-oxopent-4-en-2-ylcarbamate (5b). Compound 2 (322 mg, 1.11 mmol), 2,6-di-*tert*-butylpyridine

(249  $\mu$ L, 1.11 mmol), MeOTf (268  $\mu$ L, 2.44 mmol), 3-methyl-2-buten-1-ol (444  $\mu$ L, 4.44 mmol), n-butyl lithium (1.46 M in hexane, 3.04 mL, 4.44 mmol). Product **5b**: colorless oil, 321mg, yield 80.6%, de>49% (NMR),  $R_f = 0.78$  (Hexane:EtOAc = 1:1), HRMS (EI) calcd for C<sub>21</sub>H<sub>230</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 358.2256, found 358.2242.



Benzyl-(*R*)-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-4-methyl-1-oxopent-4-en-2ylcarbamate (5c). Compound 2 (306 mg, 1.05 mmol), 2,6-di-*tert*-butylpyridine (236  $\mu$ L, 1.05 mmol), MeOTf (254  $\mu$ L, 2.32 mmol), β-methyl allyl-alcohol (355  $\mu$ L, 4.20 mmol), n-butyl lithium (1.46 M in hexane, 2.88 mL, 4.20 mmol). Product 5c: colorless oil, 295 mg, yield 81.6%, *R<sub>f</sub>* = 0.54 (Hexane:EtOAc = 1:1), HRMS (ESI) calcd for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> (MH<sup>+</sup>) 345.2178, found 345.2166. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.14 (d, 3H, *J* = 6.5 Hz), 1.20 (d, 3H, *J* = 6.5 Hz), 1.52 (dd, 1H, *J* = 6.3, 12.2 Hz), 1.59 (dd, 1H, *J* = 6.3, 12.2 Hz), 1.75 (s, 3H), 2.08 (m, 1H), 2.23 (m, 1H), 2.33 (dd, 1H, *J* = 2.9, 14.3 Hz), 2.43 (dd, 1H, *J* = 10.7, 14.3 Hz), 4.15 (m, 1H), 4.43 (m, 1H), 4.59 (m, 1H), 4.81 (d, 2H, *J* = 6.7 Hz), 5.04 (d, 1H, *J* = 12.6 Hz), 5.07 (d, 1H, *J* = 12.6 Hz), 5.28 (d, 1H, *J* = 7.64 Hz), 7.27–7.38 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  18.54, 22.27, 22.64, 29.09, 30.83, 40.85, 50.53, 53.38, 53.80, 66.70, 114.32, 127.65, 127.91, 128.36, 136.37, 140.60, 155.97, 170.45. IR (NaCl): 3273.9, 2967.7, 1707.9, 1629.2, 1528.6, 1432.3, 1253.0.

HPLC analysis: de > 90.6% Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O: 55/45-85/15 in 25 min, 0.5 mL/min, 254 nm); retention times of the diastereomeric mixture: 12.4 min and 15.0 min (**5c**).



Benzyl-(2*R*,3*R*)-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-3-methyl-1-oxopent-4en-2-ylcarbamate (5d). Compound 2 (540 mg, 1.86 mmol), 2,6-di-*tert*-butylpyridine (418  $\mu$ L, 1.86 mmol), MeOTf (449  $\mu$ L, 4.09 mmol), crotyl alcohol (631  $\mu$ L, 7.44 mmol, trans:cis = 21.8:1), n-butyl lithium (1.46 M in hexane, 5.10 mL, 7.44 mmol). Product 5d: colorless oil, 542 mg, yield 84.6%, *R<sub>f</sub>* = 0.70 (Hexane:EtOAc = 1:1), HRMS (FAB) calcd for C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>3</sub> (MH<sup>+</sup>) 345.2178, found 345.2176. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.05 (d, 3H, *J* = 6.5 Hz), 1.15 (d, 3H, *J* = 6.3 Hz), 1.25 (d, 3H, *J* = 6.5 Hz), 1.49–1.63 (m, 2H), 2.11 (m, 1H), 2.21 (m, 1H), 2.68 (m, 1H), 4.19 (m, 1H), 4.29 (t, 1H, *J* = 9.6 Hz), 4.42 (m, 1H), 5.02–5.12 (m, 4H), 5.16 (d, 1H, *J* = 9.8 Hz), 5.82 (m, 1H), 7.27–7.42 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  17.50, 18.33, 23.24, 29.15, 30.94, 40.57, 53.15, 53.68, 56.03, 66.73, 116.32, 127.64, 127.94, 128.38, 136.43, 139.20, 156.06, 169.61. IR (NaCl): 3273.9, 2967.7, 1712.3, 1624.8, 1528.6, 1428.0, 1244.2, 1025.5.

HPLC analysis: de>86.8%, anti/syn>98:2. Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O: 50/50-70/30 in 25 min, 0.5 mL/min, 254 nm); retention times of the diastereomeric mixture: 15.0 (**5d**) min, 18.0 min (syn) and 18.7 min (**6d**).



Benzyl-(2*R*,3*R*)-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-1-oxo-3-vinylhexan-2-ylcarbamate (5e). Compound 2 (331 mg, 1.14 mmol), 2,6-di-*tert*-butylpyridine (256  $\mu$ L, 1.14 mmol), MeOTf (275  $\mu$ L, 2.51 mmol), *trans*-2-hexen-1-ol (564  $\mu$ L, 4.56 mmol), n-butyl lithium (1.46 M in hexane, 3.12 mL, 4.56 mmol). Product **5e**: colorless oil, 353 mg, yield 83.1%, *R<sub>f</sub>* = 0.73 (Hexane:EtOAc = 1:1), HRMS (EI) calcd for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 372.2413, found 372.2419. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.86 (t, 3H, *J* = 7.1 Hz), 1.07–1.44 (m, 10H), 1.51–1.62 (m, 2H), 2.06–2.25 (m, 2H), 2.48 (m, 1H), 4.19 (m, 1H), 4.31 (t, 1H, *J* = 9.8 Hz), 4.52 (m, 1H), 5.02–5.15 (m, 4H), 4.98–5.61 (m, 2H), 7.27–7.42 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  13.73, 18.20, 20.58, 23.20, 29.14, 30.87, 33.72, 46.86, 53.49, 54.01, 55.41, 66.75, 118.45, 127.56, 127.91, 128.36, 136.43, 137.72, 156.08, 170.12. IR (NaCl): 3273.9, 2967.7, 1712.3, 1629.2, 1532.9, 1432.3, 1244.2, 1034.3, 693.1.

HPLC analysis: de>85.6%, anti/syn>96:4. Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O: 55/45-85/15 in 25 min, 0.5 mL/min, 254 nm); retention times of the diastereomeric mixture: 13.0 min (**5e**), 18.1 min (syn) and 19.1 min (**6e**).



Benzyl-(2*R*,3*S*)-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-1-oxo-3-phenylpent-4-en-2-ylcarbamate (5f). Compound 2 (194 mg, 0.67 mmol), 2,6-di-*tert*-butylpyridine (150  $\mu$ L, 0.67 mmol), MeOTf (161  $\mu$ L, 1.47 mmol), cinnamyl alcohol (359 mg, 2.67 mmol), n-butyl lithium (1.40 M in hexane, 1.91 mL, 2.67 mmol). Product 5f: colorless oil 200 mg, yield 73.7%, *R*<sub>f</sub> = 0.85 (Hexane:EtOAc = 1:1), HRMS (FAB) calcd for C<sub>25</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub> (MH<sup>+</sup>) 407.2334, found 407.2339. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.59 (d, 3H, *J* = 6.5 Hz), 1.10 (d, 3H, *J* = 6.5 Hz), 1.44 (m, 2H), 1.91 (m, 1H), 2.07(m, 1H), 3.93–4.05 (m, 2H), 4.21 (m, 1H), 4.66 (t, 1H, *J* = 10.1 Hz), 5.06–5.21 (m, 4H), 5.43 (d, 1H, *J* = 10.1 Hz), 6.17 (m, 1H), 7.17–7.39 (m, 10H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  18.19, 21.91, 28.97, 30.79, 51.90, 53.03, 53.38, 56.54, 66.86, 118.28, 126.84, 127.67, 128.01, 128.42, 128.45, 128.74, 136.42, 136.89, 140.31, 156.04, 168.65. IR (NaCl): 3273.9, 2967.7, 1712.3, 1620.4, 1532.9, 1428.0, 1244.2, 1034.3, 701.8.

NMR analysis: de>93.0%, anti/syn>98:2. Chemical shift of the diastereomeric mixture: 0.60 (**5f**), 0.69 (**6f**), 6.04 (CH=, syn)

Byproduct (7) of the Meerwein salt formation and rearrangement



General procedure for the iodolactonization/zinc reduction of amides 5a-5e. Compounds 5 (0.5 mmol) were dissolved in 3 mL of THF/H<sub>2</sub>O (1.5:1). To the solution was added iodine (1.5 mmol) and the resultant mixture was stirred in the dark at ambient temperature for 3 d. The reaction was quenched by the addition of 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 mL) and was extracted with EtOAc (5 mL  $\times$  2). The combined organic layers were washed with 10% aqueous  $Na_2S_2O_3$  (3 mL  $\times$  2), saturated ammonium chloride (3 mL), brine (3 mL) and dried over MgSO<sub>4</sub>. The dry solution was concentrated in vacuo, and the crude product was purified by flash column chromatography (Hexane:EtOAc = 8:1-3:1) to afford iodolactones 8 and 9. Iodolactones 8 and 9 were then dissolved in glacial acetic acid (3 mL) and treated with zinc dust (5 mmol). The mixture was heated and kept at 65 °C with stirring for 2 h. It was then cooled to rt and 0.5 M HCl (5 mL) was added. The mixture was extracted with DCM (4 mL  $\times$  3) and washed with H<sub>2</sub>O (4 mL  $\times$  2). Then the combined organic layers were extracted with 1 M LiOH (4 mL  $\times$  3). The combined aqueous layers were washed with  $CHCl_3$  (3 mL  $\times$  3) and acidified to pH = 1 with 1M HCl. Then DCM  $(4 \text{ mL} \times 3)$  was used to extract the products from the aqueous phase. The combined organic layers were washed with water (3 mL  $\times$  2), dried over MgSO<sub>4</sub>, concentrated at rt under reduced pressure to give the final products 10.



(*R*)-2-(benzyloxycarbonylamino)pent-4-enoic acid (10a). Compound 5a (150 mg, 0.46 mmol), iodine (346 mg, 1.36 mmol), zinc dust (298 mg, 4.55 mmol). Compound 10a: colorless oil, 90 mg, yield: 70.7%,  $R_f = 0.41$  (Hexane:EtOAc:AcOH = 25:25:1),  $[\alpha]^{25.8}{}_{\rm D} -11.5$  (*c* 1.00, CHCl<sub>3</sub>), HRMS (FAB) calcd for C<sub>13</sub>H<sub>16</sub>NO<sub>4</sub> (MH<sup>+</sup>) 250.1079, found 250.1075. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.47–2.71 (m, 2H), 4.48 (q, 1H, *J* = 6.3 Hz), 5.09–5.19 (m, 4H), 5.22 (d, 1H, *J* = 7.6 Hz), 5.70 (m, 1H), 7.28–7.38 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  36.33, 53.07, 67.21, 119.74, 128.08, 128.21, 128.49, 131.64, 135.98, 155.88, 176.40. IR (NaCl): 3326.4, 2923.9, 1716.7, 1524.2, 1261.7, 1218.0, 1056.1.

HPLC analysis: ee>82.2%, Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O/MeOH: 30/70/10, 0.6 mL/min, 254 nm); retention times of the racemic mixture: 13.4 min and 14.9 min (**10a**).



(*R*)-2-(benzyloxycarbonylamino)-3,3-dimethylpent-4-enoic acid (10b). Compound **5b** (198 mg, 0.55 mmol), iodine (420 mg, 1.65 mmol), zinc dust (361 mg, 5.50 mmol). Compound **10b**: colorless oil, 100 mg, yield: 65.4%,  $R_f = 0.49$  (Hexane:EtOAc:AcOH = 25:25:1),  $[\alpha]^{24.5}_{D}$  –1.7 (*c* 4.00, MeOH), HRMS (FAB) calcd for C<sub>15</sub>H<sub>20</sub>NO<sub>4</sub> (MH<sup>+</sup>) 278.1392, found 278.1387. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.13 (s, 3H), 1.14 (s, 3H), 4.23 (d, 1H, *J* = 9.4 Hz), 5.03–5.16 (m, 4H), 5.26 (d, 1H, *J* = 9.4

Hz), 5.83 (dd, 1H, J = 10.9, 17.4 Hz), 7.26–7.43 (m, 5H), 9.75 (br, 1H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  23.68, 24.19, 40.15, 61.36, 67.25, 114.39, 128.12, 128.19, 128.48, 135.99, 142.37, 156.11, 175.83. IR (NaCl): 3317.6, 2976.4, 1716.7, 1532.9, 1419.2, 1336.1, 1244.2, 1069.3.

HPLC analysis: ee>40.1%, Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O/MeOH: 35/55/10, 0.5 mL/min, 254 nm); retention times of the racemic mixture: 12.5 min (**10b**) and 15.1 min.



(*R*)-2-(benzyloxycarbonylamino)-4-methylpent-4-enoic acid (10c).

Compound **5c** (176 mg, 0.51 mmol), iodine (389 mg, 1.5 mmol), zinc dust (334 mg, 5.10 mmol). Compound **10c**: colorless oil, 101 mg, yield: 74.4%,  $R_f = 0.45$  (Hexane:EtOAc:AcOH = 25:25:1),  $[\alpha]^{24.3}_{D}$  –5.8 (*c* 1.18, MeOH), HRMS (FAB) calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>4</sub> (MH<sup>+</sup>) 264.1236, found 264.1232. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.74 (s, 3H), 2.42 (dd, 1H, *J* = 9.0, 14.0 Hz), 2.61 (dd, 1H, *J* = 4.8, 14.2 Hz), 4.48 (m, 1H), 4.77 (s, 1H), 4.86 (s, 1H), 5.08–5.17 (m, 3H), 7.28–7.38 (m, 5H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  21.73, 40.26, 52.01, 67.15, 114.85, 127.98, 128.10, 128.41, 135.97, 139.99, 156.03, 176.84. IR (NaCl): 3322.0, 2954.6, 1716.7, 1524.2, 1344.8, 1244.2, 1051.8. HPLC analysis: ee>88%, Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O/MeOH: 23/67/10, 0.5 mL/min, 254 nm); retention times of the racemic mixture: 20.5 min and 21.7 min (**10c**).



# (2*R*,3*R*)-2-(benzyloxycarbonylamino)-3-methylpent-4-enoic acid (10d).

Compound **5d** (141 mg, 0.41 mmol), iodine (312 mg, 1.23 mmol), zinc dust (268 mg, 4.10 mmol). Compound **10d**: colorless oil, 70 mg, yield: 65.1%, anti:syn>98:2 (NMR),  $R_f = 0.44$  (CHCl<sub>3</sub>:MeOH:AcOH = 90:10:3),  $[\alpha]^{26.2}_{D}$  –6.0 (*c* 0.70, MeOH), HRMS (ESI) calcd for C<sub>14</sub>H<sub>18</sub>NO<sub>4</sub> (MH<sup>+</sup>) 264.1236, found 264.1234. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.13 (d, 3H, *J* = 6.7 Hz), 2.85 (m, 1H), 4.40 (dd, 1H, *J* = 4.4, 8.6 Hz), 5.08–5.16 (m, 4H), 5.20 (d, 1H, *J* = 8.6 Hz), 5.69 (m, 1H), 7.26–7.42 (m, 5H), 10.76 (br,1H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>)  $\delta$  16.04, 39.64, 58.02, 67.26, 117.39, 128.08, 128.19, 128.48, 135.98, 136.98, 156.36, 176.46. IR (NaCl): 3326.4, 2976.4, 1712.3, 1519.8, 1410.5, 1344.8, 1218.0, 1069.3.

HPLC analysis: ee>86.6%, Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O/MeOH: 35/55/10, 0.5 mL/min, 254 nm); retention times of the racemic mixture: 10.2 min and 14.6 min (**10d**).



(2*R*,3*R*)-2-(benzyloxycarbonylamino)-3-vinylhexanoic acid (10e). Compound 5e (185 mg, 0.50 mmol), iodine (378 mg, 1.50 mmol), zinc dust (325 mg, 5.00 mmol). Compound 10e: colorless oil, 96 mg, yield: 66.4%, anti:syn>98:2 (NMR),  $R_f = 0.55$  (Hexane:EtOAc:AcOH = 25:25:1), [α]<sup>27.0</sup><sub>D</sub> –29.4 (*c* 1.00, MeOH), HRMS (ESI) calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub> (MH<sup>+</sup>) 314.1368, found 314.1366. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.89 (d, 3H, *J* = 7.1 Hz), 1.17–1.53 (m, 4H), 2.64 (m, 1H), 4.46 (br, 1H), 4.99–5.28 (m, 5H), 5.54 (m, 1H), 7.26–7.42 (m, 5H), 10.11 (br,1H); <sup>13</sup>C (125 MHz, CDCl<sub>3</sub>) δ 13.87, 20.18, 32.56, 45.52, 57.14, 67.24, 118.56, 128.07, 128.19, 128.49, 136.01, 156.35, 176.83. IR (NaCl): 3330.7, 2958.9, 2923.9, 1712.3, 1524.2, 1414.8, 1344.8, 1257.4, 1222.4, 1051.8.

HPLC analysis: ee>89%, Chiralpak AD-RH column (CH<sub>3</sub>CN/H<sub>2</sub>O/MeOH: 42/48/10, 0.5 mL/min, 254 nm); retention times of the racemic mixture: 9.3 min and 13.3 min (**10d**).



(2R,3S)-2-(benzyloxycarbonylamino)-3-phenylpent-4-enoic acid (10f). Compound 5f (123 mg, 0.30 mmol) was dissolved in dry THF (2 mL) in a 10-mL flask under argon atmosphere. The solution was cooled to 0 °C and a pre-generated LiAlH(OMe)<sub>3</sub> (0.5 M in THF, 2.4 mL, 1.20 mmol) solution was added dropwise in four portions via a syringe over a period of 1.5 h. Upon completion of the addition, the mixture was warmed up to rt over 1.5 h and then cooled to 10 °C. Then dry tert-butyl alcohol (3 mL) was added to the solution dropwise. This was followed by the addition of 2methyl-2-butene (232  $\mu$ L), and a solution of sodium chlorite (68 mg, 0.6 mmol) in water (0.4 mL) and AcOH (1 mL). The mixture was allowed to warm up to ambient temperature with stirring. When the reaction was complete as indicated by TLC, the volatiles were removed under reduced pressure and the residue was dissolved in DCM (10 mL). The DCM was extracted with 1 M LiOH (4 mL  $\times$  3). The combined aqueous layers were washed with  $CHCl_3$  (3 mL × 3) and acidified to pH = 1 with 1M HCl. Then DCM (4 mL  $\times$  3) was used to extract the product. The combined organic layers were washed with water (3 mL  $\times$  2), dried over MgSO<sub>4</sub>, concentrated under reduced pressure at rt to give the crude product 10f. Purification of the crude product by flash column chromatography (Hexane: EtOAc:AcOH = 75:25:2) afforded 71 mg of 11f as a colorless oil. Yield: 66.4%, anti:syn>98:2 (NMR),  $R_f = 0.36$  (CHCl<sub>3</sub>:MeOH:AcOH = 90:5:1.5),  $[\alpha]^{27.5}_{D}$  +33.1 (c 0.86, MeOH), HRMS (FAB) calcd for C<sub>19</sub>H<sub>20</sub>NO<sub>4</sub> (MH<sup>+</sup>) 326.1392, found 326.1387.

HPLC analysis: ee>92.8%, Chiralpak AD-RH column (solvent A, CH<sub>3</sub>CN; solvent B, H<sub>2</sub>O; Solvent C, MeOH; gradient: 35%-45% A in 25 min, 10% C, 0.5 mL/min, 254 nm); retention times of the racemic mixture: 15.4 min and 24.3 min (**10f**).

The  ${}^{1}$ H and  ${}^{13}$ C NMR spectra for compounds 2, 5 and 10. Note: rotamers were observed in NMR spectra of 10.





















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