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Synthesis of (–)-Bulgecinine and 5-*epi*-Bulgecinine through Proline-Catalysed Asymmetric α-Hydroxylation of an Aldehyde Derived from L-Glutamic Acid

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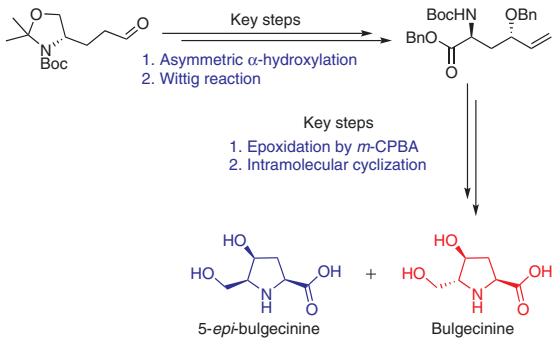

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Abstract A very efficient synthetic route to (–)-bulgecinine and 5-epibulgecinine from an aldehyde derived from L-glutamic acid is reported. Proline-catalysed asymmetric α-hydroxylation reaction of an aldehyde is the key step in this synthesis, which is used to incorporate a hydroxyl group at the α-position to that aldehyde in good yield and with very high diastereoselectivity. Both (–)-bulgecinine and 5-*epi*-bulgecinine are synthesised from the same olefin via epoxidation followed by $BF_3{\cdot}OEt_2$-catalyzed intramolecular cyclisation. This synthetic route can easily be extended for the synthesis of the enantiomer and other isomers of bulgecinine starting from an aldehyde derived from D-glutamic acid.

Key words asymmetric hydroxylation, organocatalysis, diastereoselectivity, glycopeptide, antibiotics

(–)-Bulgecinine is a nonproteinogenic amino acid that is a constituent of naturally occurring antibiotic glycopeptides known as the bulgecins; it was first isolated from *Pseudomonas acidophila* and *Pseudomonas mesoacidophila*.[1,2] Although the bulgecins by themselves show very little antibiotic activity, in combination with β-lactam antibiotics, their antibacterial activities against various Gram-negative microorganisms are greatly enhanced.[3,4] When bulgecins interact with two penicillin-binding proteins, PBP-2 and PBP-3, they induce bulge formation in the cell wall of Gram-negative bacteria in association with β-lactam antibiotics. The bulge formation is responsible for efficient killing of bacteria even at low concentrations of antibiotics. The structure of bulgecinine can be considered as a derivative of proline, having an additional hydroxy and hydroxymethylene substituents at positions 4 and 5 of the pyrrolidine ring, respectively, and it is designated as (2*S*,4*S*,5*R*)-4-hydroxy-5-hydroxymethyl proline.[4] The structures of bulgecin C and (+)- and (–)-bulgecinine are shown in Figure 1.

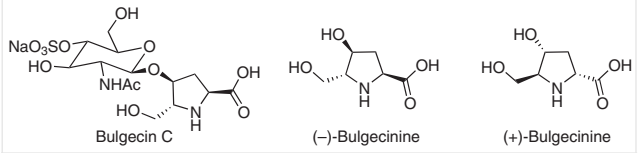


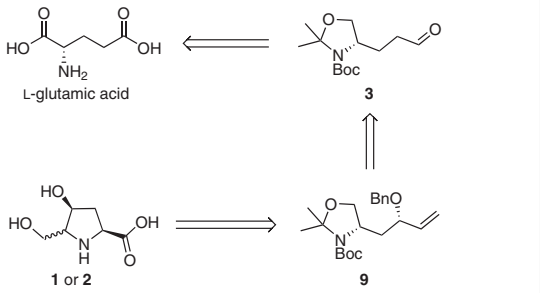
Figure 1

Given its biological activities[5–7] and structural aspects, various total syntheses of bulgecinine have been reported over the last two decades.[8–18] In spite of these methods being available, the development of a new synthetic approach is always valid in terms of the use of readily available starting materials and the possibility of preparing structurally diverse analogues. We report here an alternative method to effectively synthesise (–)-bulgecinine and 5-*epi*-(–)-bulgecinine from an aldehyde derived from L-glutamic acid using proline-catalysed asymmetric α-hydroxylation and $BF_3{\cdot}OEt_2$-mediated intramolecular epoxide ring opening with an amine as the key steps.

Proline-catalysed asymmetric α-hydroxylation of an aldehyde using nitrosobenzene followed by reduction of the N–O bond is an attractive method to incorporate a hydroxyl group stereoselectively.[19,20] To avoid racemisation of the α-centre, the aldehyde function is generally reduced to an alcohol prior to the reductive cleavage of the N–O bond. As part of our ongoing interest in the synthesis of various bioactive and natural occurring molecules,[21,22] we recently reported a successful application of this reaction to synthe-

sise D-*threo*-sphinganine, L-*erythro*-sphinganine and (–)-spisulosine from a higher homologue of Garner's aldehyde.[22]

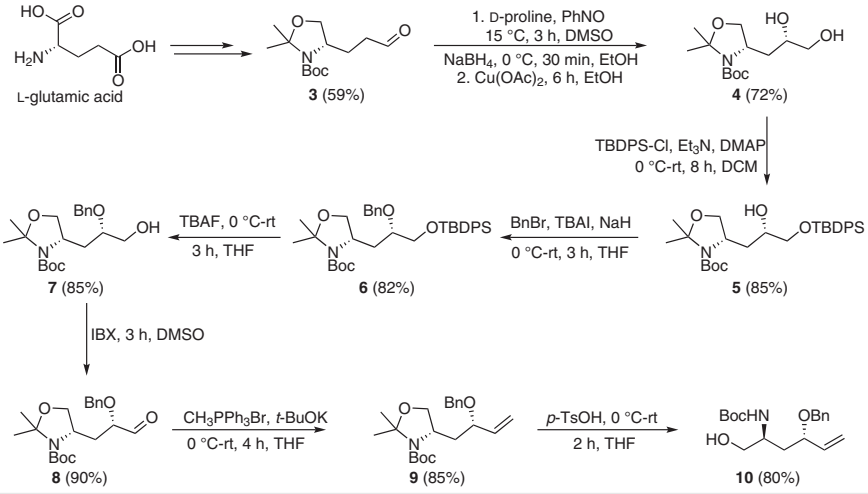
Our strategy towards the synthesis of **1** and **2** is based on the use of aldehyde **3**, which was derived from L-glutamic acid (Scheme 1). This could be readily converted into compound **9** in six steps using proline-catalysed asymmetric α-hydroxylation and a Wittig reaction as the key steps. Epoxidation using *m*-CPBA and intramolecular epoxide ring opening with an amine in the presence of $BF_3{\cdot}OEt_2$ would yield compounds **1** and **2**, as shown in Scheme 1.



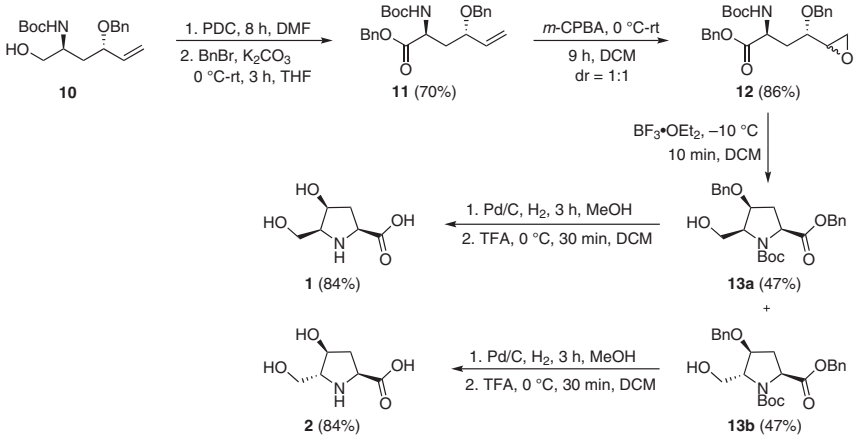
Scheme 1 Retrosynthesis of compounds **1** and **2** from **3**

The required starting material **3** is commercially available or can be readily synthesised from L-glutamic acid.[23–25] Aldehyde **3** was then subjected to diastereoselective α-hydroxylation using nitrosobenzene, and D-proline as catalyst and the product was subsequently reduced to the corresponding primary alcohol with $NaBH_4$ in one pot. The crude product was further subjected to N–O bond cleavage using $Cu(OAc)_2$ to obtain the diol **4** in 72% overall yield. It was determined by HPLC analysis that the α-hydroxylation reaction proceed with very high diastereoselectivity (dr = 92:8). The primary hydroxyl group in **4** was protected as a TBDPS ether to furnish **5**, which was then treated with benzyl bromide and NaH in the presence of tetrabutylammonium iodide (TBAI) to produce the fully protected compound **6** in 70% overall yield. The silyl protecting group in compound **6** was then selectively removed using tetrabutylammonium fluoride (TBAF) to give the corresponding primary alcohol **7** in 85% yield. Alcohol **7** was then oxidised to aldehyde **8** with 2-iodoxybenzoic acid (IBX) in 90% yield, and Wittig reaction of aldehyde **8** with methyltriphenylphosphonium bromide in the presence of *t*-BuOK yielded olefin **9** in 85% yield. The oxazolidine ring in compound **9** was deprotected using a catalytic amount of *p*-TsOH to result in amino alcohol **10** in 80% yield, as shown in Scheme 2.

Pyridinium dichromate (PDC) in DMF was used to oxidise the primary alcohol in **10** to carboxylic acid, followed by esterification with benzyl bromide in the presence of K_2CO_3 as base to give **11** in 70% overall yield (Scheme 3). Epoxidation of olefin **11** using *m*-CPBA gave a mixture of epoxides **12** (86%) in equal amounts (as judged by ^1H NMR spectroscopic analysis), which were not separable by using column chromatography. The mixture of diastereomeric epoxides was thus further subjected to $BF_3{\cdot}OEt_2$-catalysed intramolecular epoxide ring opening with the *N*-Boc amino group to furnish pyrrolidines **13a** and **13b**, each in 47% yield after separation by column chromatography. Subsequent transformations were independently carried out in each series. Hydrogenolysis of both the benzyl groups using Pd/C under hydrogen and deprotection of the Boc group using TFA furnished the target molecules 5-*epi*-(–)-bulgecinine (**1**) and (–)-bulgecinine (**2**) from **13a** and **13b**, respectively, in 84% overall yield (Scheme 3).



Scheme 2 Synthesis of compound **10** from aldehyde 3



Scheme 3 Synthesis of 5-*epi*-bulgecinine (**1**) and bulgecine (**2**)

In conclusion, an efficient synthetic route to (–)-bulgecinine and 5-*epi*-(–)-bulgecinine from an aldehyde derived from L-glutamic acid is reported. Proline-catalysed asymmetric α-hydroxylation of an aldehyde is the key step in this synthesis, being used to incorporate a hydroxyl group at the α-position of the aldehyde in good yield and with very high diastereoselectivity. All the reactions were straightforward, high yielding and proceeded under mild conditions. Both (–)-bulgecinine and 5-*epi*-(–)-bulgecinine were synthesised from the same olefin via epoxidation followed by $BF_3{\cdot}OEt_2$ mediated intramolecular epoxide ring opening with an amine. This synthetic route can be readily extended to the synthesis of (+)-bulgecinine and its isomers starting from the corresponding aldehyde derived from D-glutamic acid.

All commercially available reagents were used directly without any further purification. All reactions were carried out in anhydrous solvents and under an inert atmosphere unless otherwise mentioned. Yields are reported for compounds purified by using column chromatography. All the reactions were monitored by analytical thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualising agent and ninhydrin, 5% H_2SO_4 as a staining agent. Column chromatography was performed using Merck silica gel (particle size 60–120 and 100–200 mesh) and appropriate mixtures of petroleum ether and EtOAc were used as eluent. ^{1}H NMR spectra were recorded at 400 or 500 MHz, using Jeol spectrometers; ^{13}C NMR spectra were recorded at 100 or 125 MHz. Chemical shifts are reported in parts per million (ppm) and coupling constants in hertz (Hz). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), multiplet (m), and broad singlet (bs). IR spectra were recorded as thin films for liquids and as KBr pellets for solids. High-resolution mass spectra were recorded with a Waters Q/Tof Premier micromass HAB 213 spectrometer with an ESI source. Specific rotations were measured using a 6.0 mL cell with a 10 dm path length and are reported as $[\alpha]_D^{25}$. The diastereoselectivity of the α-hydroxylation step was determined by HPLC using an OD-H column and eluting with 6% isopropanol and hexane with a 0.5 mL min^{-1} flow rate.

Procedure for Asymmetric α-Hydroxylation of Aldehyde 3

To a stirred solution of the aldehyde **3** (1.00 g, 3.88 mmol) and nitrosobenzene (0.45 g, 4.27 mmol) in anhydrous DMSO (10 mL), D-proline (0.13 g, 1.16 mmol, 30 mol%) was added at 15 °C. The mixture was stirred vigorously until the colour changed from deep green to orange-red (ca. 3 h). The reaction mixture was brought to 0 °C and $NaBH_4$ (0.17 g, 4.65 mmol) in EtOH (15 mL) was added to the cooled solution and the mixture was stirred vigorously for 30 min. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated.

The crude product was taken to the next step, leading to the cleavage of the O–N bond. $Cu(OAc)_2$ (0.18 g, 1.00 mmol) was added to a stirred solution of the above product (1.23 g, 3.35 mmol) in EtOH (15 mL) and the reaction was monitored using TLC. After completion of the reaction (ca. 6 h), the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

***tert*-Butyl-(*S*)-4-((*S*)-2,3-Dihydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (4)**

Column chromatography (60:40, petroleum ether/EtOAc).

Yield: 0.77 g (72%); colourless oil; $[\alpha]_D^{27}$ –10.50 (c 0.20, $CHCl_3$).

IR (Thin film): 3406, 2978, 1696, 1668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.25–4.21 (m, 1 H), 4.02–3.99 (m, 1 H), 3.67–3.56 (m, 3 H), 3.50–3.46 (m, 1 H), 1.70–1.53 (m, 2 H), 1.50, 1.49 (s, 15 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.3, 93.9, 81.4, 68.5, 68.4, 66.5, 54.1, 39.1, 28.4, 28.0, 24.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$calcd for $C_{13}H_{25}NNaO_5$: 298.1630; found: 298.1632.

Procedure for *O*-TBDPS Protection

Compound **4** (1.00 g, 3.63 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL), the solution was cooled to 0 °C and triethylamine (1.01 mL, 7.26 mmol) added slowly. TBDPSCl (1.09 mL, 3.99 mmol) and DMAP (0.08 g, 0.72 mmol) were added to the above solution and the mixture was stirred well at r.t. for 8 h. After completion of the reaction as ob-

served by TLC, the reaction was quenched with saturated aqueous citric acid (20 mL), extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl (*S*)-4-((*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (5)

Column chromatography (80:20, petroleum ether/EtOAc).

Yield: 1.58 g (85%); colourless oil; $[\alpha]_D^{27}$ +5.81 (c 0.53, $CHCl_3$).

IR (thin film): 3442, 2932, 2859, 1696, 1668, 1473 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.67–7.65 (m, 4 H), 7.42–7.35 (m, 6 H), 4.19–4.15 (m, 1 H), 4.01–3.93 (m, 1 H), 3.79–3.69 (m, 3 H), 3.61–3.58 (m, 1 H), 1.98–1.92 (m, 1 H), 1.68–1.65 (m, 1 H), 1.54, 1.49 (s, 15 H), 1.06 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.7, 135.7, 133.6, 129.7, 127.8, 93.5, 80.9, 69.1, 68.4, 67.8, 54.8, 38.9, 28.5, 27.8, 26.9, 24.6, 19.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$calcd for $C_{29}H_{43}NNaO_5Si$: 536.2808; found: 536.2802.

Procedure for *O*-Benzyl Protection

Silyl protected alcohol **5** (1.00 g, 1.94 mmol) was dissolved in a two-neck round-bottom flask under nitrogen in anhydrous THF (10 mL) and benzyl bromide (0.27 mL, 2.32 mmol) and TBAI (0.21 g, 0.58 mmol) were added to the solution. The solution was cooled to 0 °C and NaH (0.10 g, 2.53 mmol) was added and the mixture was stirred at r.t. for 3 h. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), extracted with EtOAc (2 × 30 mL) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl-(*S*)-4-((*S*)-2-(Benzyloxy)-3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2,2-dimethyloxazolidine-3-carboxylate (6)

Column chromatography (90:10, petroleum ether/EtOAc).

Yield: 0.96 g(82%); colourless oil; $[\alpha]_D^{27}$ –4.39 (c 0.52, $CHCl_3$).

IR (thin film): 3393, 2932, 2859, 1696, 1454 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.69–7.65 (m, 4 H), 7.41–7.25 (m, 11 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.90–3.36 (m, 6 H), 2.04–1.71 (m, 2 H), 1.54–1.37 (m, 15 H), 1.06, 1.03 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.3, 151.6, 138.9, 138.6, 136.0, 135.9, 135.7, 133.4, 129.8, 128.4, 127.8, 93.4, 92.9, 80.0, 79.5, 79.0, 72.5, 72.2, 68.5, 66.9, 66.6, 56.5, 56.3, 36.7, 35.9, 29.8, 28.5, 27.7, 26.9, 24.7, 23.3, 19.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{36}H_{50}NO_5Si$: 604.3458; found: 604.3456.

Procedure for *O*-TBDPS Deprotection

Tetrabutyl ammonium fluoride (1 M in THF, 1.98 mL, 1.98 mmol) was added to a stirred solution of compound **6** (1.00 g, 1.65 mmol) in anhydrous THF (15 mL) at 0 °C and the mixture stirred at r.t. for 3 h. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous NH_4Cl (30 mL), extracted with EtOAc (2 × 30 mL) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl (*S*)-4-((*S*)-2-(Benzyloxy)-3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (7)

Column chromatography (70:30, petroleum ether/EtOAc).

Yield: 0.51 g (85%); colourless oil; $[\alpha]_D^{27}$ +10.61 (c 0.93, $CHCl_3$).

IR (thin film): 3446, 2977, 2932, 2871, 1696, 1669, 1454 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.25 (m, 5 H), 4.65–4.51 (m, 2 H), 4.44 (bs, 1 H), 4.21–4.16 (m, 1 H), 3.99–3.70 (m, 3 H), 3.46–3.44 (m, 2 H), 1.84–1.78 (m, 1 H), 1.62–1.55 (m, 1 H), 1.52 (s, 3 H), 1.47 (s, 12 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.9, 138.3, 128.4, 127.8, 127.6, 93.7, 81.0, 74.2, 73.4, 68.4, 67.4, 66.6, 60.7, 56.7, 54.5, 39.4, 29.7, 28.4, 27.9, 24.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{31}NNaO_5$: 388.2100; found: 388.2101.

Procedure for Primary Alcohol Oxidation

IBX (0.91 g, 3.28 mmol) was added to a solution of **7** (1.00 g, 2.73 mmol) in DMSO (10 mL) and the mixture stirred at r.t. for 3 h. After the completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with EtOAc (2 × 30 mL) and the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl (*S*)-4-((*S*)-2-(Benzyloxy)-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (8)

Column chromatography (80:20, petroleum ether/EtOAc).

Yield: 0.89 g (90%); colourless oil; $[\alpha]_D^{27}$ –12.65 (c 0.31, $CHCl_3$).

IR (thin film): 2924, 2854, 1734, 1696, 1455 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.61 (s, 1 H), 7.33 (bs, 5 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 4.02–3.88 (m, 3 H), 3.74 (bs, 1 H), 2.19–1.75 (m, 2 H), 1.55, 1.52 (s, 3 H), 1.47, 1.42 (s, 12 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 202.4, 152.5, 137.3, 128.7, 128.3, 93.7, 93.3, 82.6, 80.4, 72.9, 68.1, 55.8, 33.5, 29.8, 28.5, 27.8, 24.6.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{20}H_{30}NO_5$: 364.2124; found: 364.2128.

Procedure for Wittig Reaction

To a solution of methyl triphenyl phosphonium bromide (1.96 g, 5.50 mmol), and *t*-BuOK (0.58 g, 5.22 mmol) in anhydrous THF (20 mL), aldehyde **8** (1.0 g, 2.75 mmol) was added slowly at 0 °C and the mixture stirred at r.t. for 4 hours. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl (*S*)-4-((*S*)-2-(Benzyloxy)but-3-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (9)

Column chromatography (90:10, petroleum ether/EtOAc).

Yield: 0.84 g (85%) colourless oil; $[\alpha]_D^{27}$ –12.58 (c 0.86, $CHCl_3$).

IR (thin film): 2978, 2933, 2869, 1698, 1496 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.25 (m, 5 H), 5.74–5.72 (m, 1 H), 5.27–5.18 (m, 2 H), 4.57–4.48 (m, 1 H,), 4.30–4.27 (m, 1 H), 4.00–3.79 (m, 3 H), 3.71 (bs, 1 H), 2.03–1.80 (m, 2 H), 1.51, 1.43 (s, 15 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.1, 151.6, 138.5, 128.4, 127.7, 127.6, 118.0, 117.6, 115.4, 93.4, 92.8, 80.1, 79.6, 70.1, 68.1, 56.5, 55.9, 39.7, 38.8, 28.5, 27.6, 26.8, 24.7, 23.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{32}NO_4$: 362.2331; found: 362.2331.

Procedure for Oxazolidine Deprotection

p-TsOH (0.79 g, 4.15 mmol) was added to a stirred solution of compound **9** (1.00 g, 2.76 mmol) in MeOH (20 mL) at 0 °C and the mixture stirred at r.t. for 2 h. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The MeOH was removed under reduced pressure, the aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

tert-Butyl ((2*S*,4*S*)-4-(Benzyloxy)-1-hydroxyhex-5-en-2-yl)carbamate (10)

Column chromatography (70:30, petroleum ether/EtOAc).

Yield: 0.71 g (80%); colourless oil; $[\alpha]_D^{27}$ –23.79 (c 0.93, $CHCl_3$).

IR (thin film): 3407, 2976, 2929, 1690, 1499 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.25 (m, 5 H), 5.79–5.70 (m, 1 H), 5.28–5.23 (m, 3 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.30 (d, *J* = 12.0 Hz, 1 H), 3.93–3.82 (m, 2 H), 3.59 (bs, 2 H,), 2.98 (bs, 1 H), 1.82–1.75 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.4, 138.0, 128.5, 128.2, 127.8, 117.6, 79.5, 78.1, 70.7, 65.8, 50.5, 37.0, 29.8, 28.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{27}NNaO_4$: 344.1838; found: 344.1830.

Procedure Primary Alcohol Oxidation

Pyridinium dichromate (11.71 g, 31.13 mmol) was added to a stirred solution of alcohol **10** (1.00 g, 3.11 mmol) in DMF (30 mL) and the mixture was stirred at r.t. for 8 h. After completion of the reaction as observed by TLC, the reaction was quenched with water (300 mL) and the mixture was extracted with EtOEt (2 × 50 mL). The combined organic phases were further extracted with saturated aqueous $NaHCO_3$ (2 × 30 mL). The combined aqueous extracts containing the carboxylate salt were combined, acidified with saturated aqueous $KHSO_4$ and extracted with Et_2O (2 × 50 mL). The ether layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude product (0.82 g, 2.44 mmol) was dissolved in anhydrous THF and the mixture was cooled to 0 °C. Benzyl bromide (0.37 mL, 3.17 mmol) and K_2CO_3 (0.50 g, 3.66 mmol) were then added and the mixture was stirred at r.t. for 3 h. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

Benzyl (2*S*,4*S*)-4-(Benzyloxy)-2-((*tert*-butoxycarbonyl)amino)hex-5-enoate (11)

Column chromatography (90:10, petroleum ether/EtOAc).

Yield: 0.91 g (70%); colourless oil; $[\alpha]_D^{27}$ –4.65 (c 0.73, $CHCl_3$).

IR (thin film): 3412, 2976, 1716, 1497, 1454 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.34–7.25 (m, 10 H), 5.73–5.63 (m, 2 H), 5.24–5.04 (m, 4 H), 4.54–4.50 (m, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.19 (d, *J* = 12.0 Hz, 1 H), 3.76–3.71 (m, 1 H), 2.08–1.91 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.4, 155.7, 137.9, 137.5, 135.7, 128.6, 128.5, 128.5, 128.4, 128.2, 127.8, 118.0, 79.6, 78.3, 70.8, 66.9, 51.9, 37.3, 29.8, 28.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}NNaO_5$: 448.2100; found: 448.2107.

Procedure for Alkene Epoxidation

m-Chloroperbenzoic acid (50–55%, 0.81 g, 4.70 mmol) was added to a stirred solution of alkene **11** (1.0 g, 2.35 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred at r.t. for 9 h. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous Na_2SO_3 (30 mL) and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

Benzyl (2*S*,4*S*)-4-(Benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-(oxiran-2-yl)butanoate (12)

Column chromatography (80:20, petroleum ether/EtOAc).

Yield: 0.89 g (86%); colourless oil; $[\alpha]_D^{27}$ –5.78 (c 0.38, $CHCl_3$).

IR (thin film): 3380, 2925, 2854, 1715, 1455 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.25 (m, 10 H), 5.59 (d, *J* = 8.0 Hz, 1 H), 5.46 (d, *J* = 8.0 Hz, 1 H), 5.22–5.02 (m, 2 H), 4.77–4.36 (m, 3 H), 3.25–2.83 (m, 2 H), 2.75–2.59 (m, 2 H), 2.24–1.92 (m, 3 H), 1.41 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.4, 155.6, 137.8, 135.5, 135.5, 128.7, 128.6, 128.5, 128.5, 128.3, 128.0, 127.9, 79.7, 78.6, 76.0, 73.1, 72.5, 67.1, 54.5, 53.0, 51.5, 51.3, 46.0, 42.8, 34.7, 33.8, 29.8, 28.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}NNaO_6$: 464.2049; found: 464.2041.

Note: Additional peaks observed in the NMR spectra at r.t. are due to the existence of rotamers.

Procedure for Epoxide Ring Opening Reaction

$BF_3{\cdot}OEt_2$ (50% solution, 0.037 mL, 0.14 mmol) dissolved in anhydrous CH_2Cl_2 (0.50 mL) was added to a stirred solution of compound **12** (0.13 g, 0.29 mmol) in anhydrous CH_2Cl_2 (6 mL) at –10 °C under nitrogen and reaction mixture was stirred for 10 min at the same temperature. After completion of the reaction as observed by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography.

2-Benzyl 1-(*tert*-Butyl) (2*S*,4*S*,5*S*)-4-(Benzyloxy)-5-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (13a)

Column chromatography (60:40, petroleum ether/EtOAc).

Yield: 0.06 g (47%) colourless oil; $[\alpha]_D^{27}$ –25.01 (c 0.65, $CHCl_3$).

IR (thin film): 3455, 2931, 1754, 1699, 1497, 1454 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.28–7.25 (m, 10 H), 5.21–4.90 (m, 2 H), 4.56–4.36 (m, 3 H), 4.16 (bs, 1 H), 4.05–3.84 (m, 1 H), 3.69 (bs, 3 H), 2.36–2.27 (m, 2 H), 1.43, 1.32 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.9, 155.7, 137.7, 135.7, 128.5, 128.4, 128.3, 127.7, 127.6, 81.1, 79.4, 70.5, 66.9, 65.9, 64.4, 59.7, 34.9, 28.4, 28.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}NNaO_6$: 464.2049; found: 464.2042.

2-Benzyl 1-(*tert*-Butyl) (2*S*,4*S*,5*R*)-4-(Benzyloxy)-5-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate (13b)

Column chromatography (60:40, petroleum ether/EtOAc).

Yield: 0.06 g (47%); colourless oil; $[\alpha]_D^{27}$ +11.18 (c 0.42, $CHCl_3$).

IR (thin film): 3417, 2930, 1732, 1698, 1497, 1455 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.25 (m, 10 H), 5.26–5.05 (m, 2 H), 4.58–4.41 (m, 2 H), 4.30–4.27 (m, 1 H), 4.18–3.87 (m, 5 H), 2.51–2.30 (m, 1 H), 2.22–2.01 (m, 1 H), 1.45, 1.32 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.3, 173.0, 154.7, 154.1, 137.5, 135.3, 128.7, 128.6, 128.4, 128.2, 128.0, 127.7, 81.1, 81.0, 72.1, 71.7, 67.2, 62.0, 60.8, 60.0, 57.7, 56.7, 34.1, 33.3, 29.8, 28.4, 28.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}NNaO_6$: 464.2049; found: 464.2043.

General Procedure for Hydrogenolysis and *N*-Boc Deprotection

To a stirred solution of compound **13** (0.06 g, 0.13 mmol) in MeOH (10 mL), 10 mol%, Pd/C (10%) was added and the mixture was stirred at r.t. for 3 h under H_2. After completion of the reaction as observed by TLC, the reaction mixture was filtered through a Celite® pad and solvent was removed under reduced pressure.

TFA (0.50 mL) was added to a stirred solution of the crude product obtained after hydrogenolysis in anhydrous CH_2Cl_2 (2 mL) at 0 °C and the solution was stirred until completion of reaction as observed by TLC. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL) and concentrated again. This was repeated four times to remove TFA and other volatile material completely from the crude product.

(2*S*,4*S*,5*S*)-4-Hydroxy-5-(hydroxymethyl)pyrrolidine-2-carboxylic Acid (1)

Yield: 0.03 g (84%); colourless oil; $[\alpha]_D^{27}$ –10.50 (c 0.50, CH_3OH).

IR (thin film): 2955, 2923, 2852, 1647 cm^{-1}.

^{1}H NMR (D_2O, 400 MHz): δ = 4.54 (bs, 1 H), 4.42 (dd, *J* = 6.5, 5.0 Hz, 1 H), 4.08–3.93 (m, 2 H), 3.75–3.72 (m, 1 H), 2.64–2.57 (m, 1 H), 2.35 (dd, *J* = 6.5, 5.0 Hz, 1 H).

^{13}C NMR (D_2O, 100 MHz): δ = 69.4, 65.8, 58.6, 57.4, 37.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_6H_{12}NO_4$: 162.0766; found: 162.0764.

(2*S*,4*S*,5*R*)-4-Hydroxy-5-(hydroxymethyl)-pyrrolidine-2-carboxylic Acid (2)

Yield: 0.03 g (84%); colourless oil; $[\alpha]_D^{27}$ –13.10 (c 0.50, CH_3OH) {Lit.[15] $[\alpha]_D^{23}$ –13.8 (c 0.21, H_2O)}.

IR (thin film): 3392, 2917, 2850, 1648 cm^{-1}.

^{1}H NMR (D_2O, 500 MHz): δ = 4.43 (q, *J* = 5.0 Hz, 1 H), 4.27 (dd, *J* = 9.0, 6.5 Hz, 1 H), 3.95 (dd, *J* = 15.0, 5.0 Hz, 1 H), 3.80–3.78 (m, 2 H), 2.72 (ddd, *J* = 13.8, 9.0, 6.8 Hz, 1 H), 2.21 (ddd, *J* = 13.8, 6.5, 5.0 Hz, 1 H).

^{13}C NMR (D_2O, 125 MHz): δ = 70.3, 66.7, 59.1, 57.8, 36.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_6H_{12}NO_4$: 162.0766; found: 162.0782.

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Supporting Information

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