Diastereoselective Synthesis of (–)-Bestatin, Epibestatin, Phebestin and (3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic Acid from an Aldehyde Derived from D-Phenylalanine

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Abstract

A convenient and efficient method for the synthesis of (–)-bestatin, epibestatin, phebestin, and (3S,4R)-4-amino-3-hydroxy-5-phenylpentanoic acid is reported. The key step is a proline-catalysed asymmetric hydroxylation of an aldehyde derived from D-phenylalanine, which leads to incorporation of a hydroxyl group at the α-position of that aldehyde with good yield and very high diastereoselectivity. Bestatin and its diastereomer epibestatin are synthesized from the same starting material using the same sequence of reactions, except for proline as the catalyst. An O-MOM and Boc-protected amino acid, a common intermediate for bestatin, was coupled with a dipeptide, H-Val-Phe-OMe followed by global deprotection to yield phebestin. (3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic acid was also synthesized in eight steps from the same starting material. The reported synthetic route offers a general method for the synthesis of such types of compounds and their analogues by changing the proline catalyst and/or the starting material from D- to L-proline.

Key words asymmetric hydroxylation, organocatalysis, reductive cleavage

(–)-Bestatin (Ubenimex) is a dipeptide containing an α-hydroxy-β-amino amide subunit that was first isolated from Streptomyces olivoreticulithec by Umezawa et al. in 1976.1,2 It is an aminopeptidase inhibitor that exhibits immunostimulatory activity as well as cytotoxic activity.3,4 It is used clinically for the treatment of cancer, HIV, hypertension, and shows potential as an anti-inflammatory agent.5–8

Structure modification studies of bestatin and similar molecules such as phebestin, a tripeptide, indicate that biological activities of these molecules are significantly influenced by the (2S)-syn-stereochemistry of the hydroxyl group.9,10 Various stereoselective methods for the synthesis of bestatin, phebestin11–27 and epibestatin28,29 are available and most of them utilized D-phenylalanine as a chiral starting material. Reported herein is an alternative and short method for the synthesis of bestatin, epibestatin, phebestin and (3S,4R)-4-amino-3-hydroxy-5-phenylpentanoic acid using proline-catalysed asymmetric α-hydroxylation of an aldehyde derived from D-phenylalanine. The structures of these compounds are shown in Figure 1.

Figure 1

Proline-catalysed α-hydroxylation of an aldehyde using nitrosobenzene followed by reduction of the N–O bond is an attractive method to introduce a hydroxyl group stereoselectively.10–32 The aldehyde functional group can be further reduced to an alcohol or converted into an alkene through Wittig reaction in order to avoid racemization at the α-position. As the part of our studies towards the synthesis of various bioactive and naturally occurring mole-
cules,\textsuperscript{32-41} we recently reported the synthesis of $D$-\textit{threo-}
spinganine, \textit{l}-\textit{erythro}-spinganine and \textit{(-)}-spisulosine from an 
aldehyde derived from aspartic acid.\textsuperscript{42}

In the retrosynthetic analysis, it was anticipated that both bestatin and epibestatin could be synthesized from \textit{acid 9} using peptide coupling followed by deprotection of the Boc and MOM groups. Diol \textit{5} could be obtained from aldehyde \textit{4} using an $\alpha$-hydroxylation reaction. Compound \textit{9a} could be converted into phebestin. Olefin \textit{15} could be obtained from aldehyde \textit{4} using an $\alpha$-hydroxylation reaction followed by Wittig reaction and would yield compound \textit{3} as shown in Scheme 1.

Aldehyde \textit{4} (for preparation see the literature\textsuperscript{41}) was subjected to diastereoselective hydroxylation using nitrosobenzene, and \textit{D}-proline as catalyst and subsequently reduced to the corresponding primary alcohol by NaBH$_4$ in one pot. The crude product was further subjected to N-O bond cleavage using Cu(OAc)$_2$ to give diol \textit{5a} in 66% yield overall. It was observed by $^1$H NMR spectroscopy that the hydroxylation reaction proceeded with 90:10 diastereoselectivity. The primary and secondary hydroxyl groups of compound \textit{5a} were protected as their TBDPS and MOM derivatives, respectively, to obtain the fully protected compound \textit{7a} in 64% overall yield. TBAF was then used to remove the silyl protecting group in compound \textit{7a} to furnish the primary alcohol \textit{8a} in 89% yield, which was then treated with PDC in DMF to produce the corresponding carboxylic acid \textit{9a} in 76% yield (Scheme 2).

The fully protected $\alpha$-hydroxy-$\beta$-amino acid \textit{9a} is the precursor for the synthesis of both bestatin and phebestin. To obtained bestatin, compound \textit{9a} was coupled with the benzyl ester of \textit{l}-leucine in the presence of EDC-HCl, HOBt and DIPEA to give the corresponding fully protected dipeptide \textit{10a} in 82% yield. Compound \textit{10a} was further subjected to Pd-catalysed hydrogenolysis followed by acetalysis of the Boc and MOM groups to furnish target molecule \textit{1a} from \textit{10a} in 86% yield (Scheme 2).

Epibestatin \textit{1b} was obtained in an overall yield of 22% from aldehyde \textit{4} using exactly the same sequence of reactions but using \textit{l}-proline in the asymmetric $\alpha$-hydroxylation reaction (Scheme 3) leading to a diastereomer ratio of 87:13 as judged by $^1$H NMR spectroscopy. Epibestatin is available in very limited quantities commercially and to date only a few synthetic strategies have been reported.\textsuperscript{28,29}

To synthesize phebestin, compound \textit{9a} was coupled with dipeptide \textit{12}, which was obtained from coupling the methyl ester of \textit{l}-phenylalanine with NH-Boc protected
L-valine, to give the fully protected tripeptide 13 in 70% yield. Hydrolysis of the methyl ester using LiOH followed by acidolysis of the Boc and MOM groups furnished the target molecule 2 in 89% yield over two steps (Scheme 4).

\[
\begin{align*}
1 & : \text{BocNH} - \text{Ph} - \text{CH}_{2} \text{OH} \\
2 & : \text{BocNH} - \text{Ph} - \text{CO}_{2} \text{Et} \\
3 & : \text{BocNH} - \text{Ph} - \text{NH}_{2} \\
4 & : \text{NHBoc} - \text{Ph} - \text{CHO} \\
5 & : \text{NHBoc} - \text{Ph} - \text{CO}_{2} \text{Et} \\
6 & : \text{NHBoc} - \text{Ph} - \text{HCl} \\
7 & : \text{NHBoc} - \text{Ph} - \text{POCl}_{3} \\
8 & : \text{NHBoc} - \text{Ph} - \text{NH}_{2} \cdot \text{HCl}
\end{align*}
\]

Scheme 4 Synthesis of phebestin (2)

β-Hydroxy-γ-amino acids have been designed for biologically active peptide mimics and for HIV protease inhibitors. Stictamide A, tasiamide B and haplostatin are biologically important compounds that contain 4-amino-3-hydroxy-5-phenylpentanoic acid as a structural fragment. The activities of such compounds depend on the stereochimistries of both the amino- and hydroxyl groups.44,45 A variety of stereoselective methods for the synthesis of these acids and their analogues is available.46–50 (3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic acid (3) was also synthesized from the same starting material 4 in eight steps and in an overall yield of 15% (Scheme 5).

Thus, aldehyde 4 was subjected to L-proline-catalysed asymmetric α-hydroxylation and subsequent Wittig reaction in one pot. The crude product was further treated with Cu(OAc)₂ leading to cleavage of the N–O bond to form olefin 15 in 70% overall yield (Scheme 5).

Both the hydroxyl and amino groups in compound 15 were protected as an oxazolidine using 2,2-dimethoxypropane (DMP) and a catalytic amount of p-TsOH to 16 in 85% yield. LiBH₄ was used to reduce compound 16 to primary alcohol 17 in 80% yield, and this was then oxidized to aldehyde 18 using 2-iodoxybenzoic acid (IBX) in 88% yield. The aldehyde 18 was subjected to L-proline-catalysed asymmetric α-hydroxylation reaction followed by reduction and N–O bond cleavage using NaBH₄ and Cu(OAc)₂, respectively, to furnish diol 19 in 65% overall yield. NaIO₄ was used to cleave the diol to produce aldehyde 20, which was further oxidised to an acid 21 using PDC in 57% yield after two steps. Acidolysis of the Boc group and oxazolidine ring in compound 21 furnished 3 in 98% yield (Scheme 5).

In conclusion, we have demonstrated a convenient and efficient route for the synthesis of bestatin, epibestatin, phebestin and (3S,4R)-4-amino-3-hydroxy-5-phenylpentanoic acid using proline-catalysed α-hydroxylation of an aldehyde derived from D-phenylalanine with high diastereo-selectivities and in good overall yields. The method described here offers a general method to synthesize several similar molecules using an organocatalytic route.

See the Supporting Information for general information.

Asymmetric α-Hydroxylation of Aldehydes; General Procedure

To a stirred solution of aldehyde 4 (1.00 g, 3.80 mmol) and nitrosobenzene (0.44 g, 4.18 mmol) in anhydrous DMSO (10 mL), d- or l-proline (0.13 g, 1.14 mmol, 30 mol%) was added at 15 °C. The mixture was stirred for 3 h at the same temperature, then cooled to 0 °C and NaBH₄ (0.28 g, 7.60 mmol) in EtOH (15 mL) was added and the mixture was stirred vigorously for 30 min at 0 °C. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NH₄Cl (30 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated. The crude amino-hydroxylated product was taken as such to the next step leading to the cleavage of O–N bond.

Cu(OAc)₂ (0.17 g, 0.96 mmol) was added to a stirred solution of the above product in EtOH (15 mL) and the mixture was stirred vigorously for 6 h at room temperature. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NH₄Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography. The same procedure was used for the preparation of compound 19.
**tert-Butyl (2R,3S)-3,4-Dihydroxy-1-phenylbutan-2-yl)carbamate (5a)**

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

Yield: 0.70 g (66%); clear oil; \([\text{IR}]) + 17.28\) (c 0.96, CHCl₃).

IR (thin film): 3434, 3070, 3027, 2927, 2856, 1689 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): \(\delta = 7.62–7.57\) (m, 4 H), 7.42–7.21 (m, 11 H), 4.93 (br s, 1 H), 3.76–3.69 (m, 2 H), 3.61–3.60 (m, 2 H), 2.96–2.85 (m, 2 H), 2.67 (br s, 1 H), 1.35 (s, 9 H), 1.04 (s, 9 H).

13C NMR (CDCl₃, 100 MHz): \(\delta = 155.9, 138.4, 135.6, 133.1, 130.0, 129.5, 128.5, 127.9, 126.4, 79.4, 71.1, 65.7, 52.7, 38.6, 29.8, 28.4, 27.0, 19.3.


**tert-Butyl (2R,3R)-4-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-1-phenylbutan-2-yl)carbamate (6b)**

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

Yield: 1.55 g (84%); clear oil; \([\text{IR}]) + 2.26\) (c 1.45, CHCl₃).

IR (thin film): 3417, 2930, 2857, 1692, 1497 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): \(\delta = 7.70–7.68\) (m, 3 H), 7.46–7.39 (m, 6 H), 7.29–7.17 (m, 6 H), 4.98 (br s, 1 H), 3.99 (br s, 1 H), 3.76–3.62 (m, 3 H), 3.08 (br s, 1 H), 2.96–2.85 (m, 2 H), 1.36 (s, 9 H), 1.11 (s, 9 H).

13C NMR (CDCl₃, 125 MHz): \(\delta = 156.0, 138.0, 135.7, 132.9, 132.8, 130.0, 129.5, 128.5, 128.0, 127.9, 126.4, 79.4, 72.6, 65.4, 54.3, 36.6, 29.8, 28.4, 27.0, 19.3.


**MOM Protection; General Procedure**

MOM chloride (0.58 mL, 7.68 mmol) followed by Hunig’s base, DIPEA (1.68 mL, 9.62 mmol) were added to a stirred solution of compound 6 (1.00 g, 1.92 mmol) in DCM (25 mL) at 0 °C, and the mixture was stirred vigorously at r.t. for 6 h. On complete disappearance of starting material, the reaction was quenched with water (20 mL), and the mixture was extracted with DCM (2 × 30 mL) and the combined organic phases were washed with 2% HCl (2 × 20 mL), dried over Na₂SO₄, filtered, concentrated and purified through column chromatography.

**tert-Butyl (2R,3S)-4-((tert-Butyldiphenylsilyl)oxy)-3-(methoxy-methoxy)-1-phenylbutan-2-yl)carbamate (7a)**

Column chromatography (petroleum ether/EtOAc, 85:15).

Yield: 0.84 g (78%); clear oil; \([\text{IR}]) + 1.65\) (c 0.48, CHCl₃).

IR (thin film): 2928, 2856, 1715, 1494 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): \(\delta = 7.53–7.47\) (m, 4 H), 7.35–7.15 (m, 11 H), 4.93 (d, \(J = 8.0 \) Hz, 1 H), 4.58–4.43 (m, 2 H), 4.09–4.04 (m, 1 H), 3.56–3.51 (m, 3 H), 3.28 (s, 3 H), 2.88–2.71 (m, 2 H), 1.33 (s, 9 H), 0.91 (s, 9 H).

13C NMR (CDCl₃, 100 MHz): \(\delta = 155.5, 135.6, 133.2, 129.7, 129.6, 128.5, 127.8, 126.3, 97.1, 79.1, 63.6, 55.9, 52.4, 38.7, 28.5, 26.8, 19.2.


**Silyl Protection; General Procedure**

Compound 5 (1.00 g, 3.55 mmol) was dissolved in anhydrous DCM (20 mL) and the solution cooled to 0 °C. TBDPSCl (1.07 mL, 3.91 mmol), DMAP (0.08 g, 0.71 mmol) and triethylamine (0.74 mL, 5.32 mmol) were added and the reaction mixture was stirred r.t. for 8 h. On complete disappearance of starting material, the reaction was quenched with saturated aqueous citric acid (20 mL), the crude product was extracted with DCM (2 × 30 mL) and the combined organic phases containing crude product were dried over Na₂SO₄, filtered, concentrated under vacuum, and purified by column chromatography.

**tert-butyl (2R,3S)-4-((tert-Butyldiphenylsilyl)oxy)-3-hydroxy-1-phenylbutan-2-yl)carbamate (6a)**

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

Yield: 1.51 g (82%); clear oil; \([\text{IR}]) + 17.28\) (c 0.96, CHCl₃).

IR (thin film): 3434, 3070, 3027, 2927, 2856, 1689 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): \(\delta = 7.62–7.57\) (m, 4 H), 7.42–7.21 (m, 11 H), 4.93 (br s, 1 H), 3.76–3.69 (m, 2 H), 3.61–3.60 (m, 2 H), 2.96–2.85 (m, 2 H), 2.67 (br s, 1 H), 1.35 (s, 9 H), 1.04 (s, 9 H).

13C NMR (CDCl₃, 100 MHz): \(\delta = 155.9, 138.4, 135.6, 133.1, 130.0, 129.5, 128.5, 127.9, 126.4, 79.4, 71.1, 65.7, 52.7, 38.6, 29.8, 28.4, 27.0, 19.3.

butan-2-yl)carbamate (8b)

were washed with saturated aqueous NaHCO₃ (2 × 30 mL) and the combined organic phases were dried over Na₂O₃. The combined organic phases were dried over Na₂O₃, filtered, concentrated under vacuum, and purified by column chromatography.

**Silyl Deprotection; General Procedure**

TBAF (1 M in THF, 1.94 mL, 1.94 mmol) was added to a stirred solution of compound 1 (0.1 g, 1.77 mmol) in anhydrous THF (15 mL) at 0 °C and the solution was stirred at r.t. for 2 h. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NH₄Cl (30 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed over Na₂O₃, filtered, concentrated under vacuum, and purified by column chromatography.

**tert-Butyl ((2R,3S)-4-Hydroxy-3-(methoxymethoxy)-1-phenylbutan-2-yl)carbamate (8a)**

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

Yield: 0.51 g (89%); clear oil; [a]₂⁷ = 42.55 (c 0.79, CHCl₃).

IR (thin film): 3471, 3368, 3021, 2964, 2929, 1692, 1523 cm⁻¹.

**3C NMR (CDCl₃, 125 MHz):** δ = 155.6, 138.4, 135.7, 135.7, 133.0, 129.9, 129.9, 129.2, 128.3, 127.8, 127.8, 126.2, 96.6, 93.6, 78.7, 64.4, 63.5, 55.7, 52.9, 38.6, 36.9, 28.4, 26.9, 19.2.


**tert-Butyl ((2R,3R)-4-Hydroxy-3-(methoxymethoxy)-1-phenylbutan-2-yl)carbamate (8b)**

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

Yield: 0.52 g (90%); clear oil; [a]₂⁷ = 42.47 (c 1.02, CHCl₃).

IR (thin film): 3471, 3368, 3201, 2964, 2929, 1692, 1523 cm⁻¹.

**1H NMR (CDCl₃, 500 MHz):** δ = 7.23–7.12 (m, 5 H), 4.71 (d, J = 10.0 Hz, 1 H), 4.67–4.53 (m, 2 H), 4.05 (dd, J = 15.0, 10.0 Hz, 1 H), 3.61 (dd, J = 10.5, 5.0 Hz, 1 H), 3.68–3.44 (m, 1 H), 3.34 (s, 3 H), 2.84–2.74 (m, 2 H), 1.33 (s, 9 H).

**13C NMR (CDCl₃, 125 MHz):** δ = 156.6, 137.9, 129.1, 128.6, 126.6, 97.7, 80.7, 80.0, 62.6, 55.9, 52.1, 38.3, 29.8, 28.4.


**Peptide Coupling of 9**

Compound 9 (0.19 g, 0.55 mmol) was dissolved in anhydrous DCM (10 mL) and the solution was cooled in an ice bath followed by addition of EDC–HCl (0.21 g, 1.12 mmol) and HOBr (0.15 g, 1.12 mmol) and then stirred for 20 min. H-Leu-OBn (0.17 g, 0.55 mmol) was added to the reaction mixture followed by DIPEA (0.20 mL, 1.23 mmol) and the mixture was stirred at r.t. for 6 h. On complete disappearance of starting material, the organic layer was washed with aqueous citric acid (3 × 15 mL) and 2 M aqueous NaHCO₃ (3 × 15 mL). The organic layers were combined, dried over Na₂O₃, filtered, concentrated, and purified by column chromatography.

**Benzyl ((2S,3R)-3-((tert-Butyroxy carbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-1-leucinate (10a)**

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

Yield: 0.24 g (82%); white solid; [a]₂⁷ = 32.23 (c 0.69, CHCl₃); mp 99–101 °C.

IR (thin film): 3333, 3277, 3063, 3030, 2961, 2929, 2873, 1748, 1688, 1650, 1547, 1524 cm⁻¹.

**1H NMR (CDCl₃, 400 MHz):** δ = 7.31–7.09 (m, 10 H), 6.96 (d, J = 8.7 Hz, 1 H), 5.19 (d, J = 9.9 Hz, 1 H), 5.11–5.04 (m, 2 H), 4.69–4.62 (m, 3 H), 4.17 (br s, 1 H), 4.06 (m, 1 H), 3.35 (s, 3 H), 2.82 (dd, J = 13.7, 5.4 Hz, 1 H), 2.59–2.54 (m, 1 H), 1.62–1.50 (m, 3 H), 1.23 (s, 9 H), 0.86 (d, J = 3.4 Hz, 6 H).

**13C NMR (CDCl₃, 125 MHz):** δ = 172.5, 170.5, 155.0, 137.8, 135.3, 129.4, 128.7, 128.6, 128.4, 128.4, 126.6, 115.5, 96.9, 79.2, 78.1, 67.2, 56.7, 53.3, 50.4, 41.5, 37.5, 29.8, 28.3, 24.9, 22.9, 21.8.
Benzyl ((2S,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxy-methoxy)-4-phenylbutanoyl)-L-leucine (11a)

Column chromatography (CH₂Cl₂/MeOH, 95:5).

Yield: 0.058 g (94%); clear oil.


(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-l-leucine (11b)

Column chromatography (DCM/MeOH, 95:5).

Yield: 0.10 g (92%); clear oil;


Acidolysis Reaction; General Procedure

HCl (6 M in EtOAc, 0.50 mL) was added to 11 (0.083 g, 0.18 mmol) or 21 (0.050 g, 0.14 mmol) at 0°C and the mixture was stirred at r.t. for 3 h. On complete disappearance of starting material, the white residue was triturated 3 to 4 times with cold EtOAc (5 mL).

(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-L-leucine (1a)

Yield: 0.058 g (94%); white solid; [α]D₂⁰ +5.82 (c 0.38, H₂O); mp 226–228 °C [lit.19 [α]D₂⁰ +5.90 (c 0.38 H₂O); mp 228–230 °C].


(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-l-valyl-L-phenylalanine (2)

Yield: 0.068 g (95%); white solid; [α]D₂⁰ +12.20 (c 1.02, H₂O); mp 187–189 °C [lit.19 [α]D₂⁰ +11.9 (c 1.00, HOAc); 188–191 °C].


(3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic Acid (3)

Yield: 0.032 g (98%); clear oil; [α]D₂⁰ -1.50 (c 0.13, MeOH).


(3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic Acid (3)

Yield: 0.032 g (98%); clear oil; [α]D₂⁰ -1.50 (c 0.13, MeOH).


Acidolysis Reaction; General Procedure

HCl (6 M in EtOAc, 0.50 mL) was added to 11 (0.083 g, 0.18 mmol), 14 (0.092 g, 0.15 mmol) or 21 (0.050 g, 0.14 mmol) at 0°C and the mixture was stirred at r.t. for 3 h. On complete disappearance of starting material, the white residue was triturated 3 to 4 times with cold EtOAc (5 mL).

(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-L-leucine (1a)

Yield: 0.058 g (94%); white solid; [α]D₂⁰ +5.82 (c 0.38, H₂O); mp 226–228 °C [lit.19 [α]D₂⁰ +5.90 (c 0.38 H₂O); mp 228–230 °C].


(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-l-valyl-L-phenylalanine (2)

Yield: 0.068 g (95%); white solid; [α]D₂⁰ +12.20 (c 1.02, H₂O); mp 187–189 °C [lit.19 [α]D₂⁰ +11.9 (c 1.00, HOAc); 188–191 °C].


(3S,4R)-4-Amino-3-hydroxy-5-phenylpentanoic Acid (3)

Yield: 0.032 g (98%); clear oil; [α]D₂⁰ -1.50 (c 0.13, MeOH).

HRMS (ESI–TOF): \(m/z\) [M + H]\(^+\) calcd for C\(_{11}\)H\(_{16}\)NO\(_3\): 210.1130; found: 210.1129.

**Synthesis of Dipeptide Boc-Val-Phe-OMe**

Boc-Val-OH (0.20 g, 0.92 mmol) was dissolved in anhydrous DCM (10 mL) and the solution was cooled in an ice bath followed by addition of EDC·HCl (0.35 g, 1.84 mmol) and HOBT (0.24 g, 1.84 mmol) and the mixture was stirred for 20 min. HCl·H\(_2\)N-OMe·H\(_2\)O (0.19 g, 0.92 mmol) was added to the reaction mixture followed by DIPEA (0.35 mL, 2.03 mmol) and the mixture was stirred at r.t. for 6 h. On complete disappearance of starting material, the organic layer was washed with aqueous citric acid (3 × 15 mL) and 2 M aqueous NaHCO\(_3\) (3 × 15 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered, concentrated under vacuum, and purified by column chromatography.

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

**Methyl (tert-Butoxycarbonyl)-l-valyl-l-phenylalaninate (12)**

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

Yield: 0.31 g (90%); white solid; \([M + H]\(^+\) calcd for C\(_{11}\)H\(_{16}\)NO\(_3\): 210.1129; found: 210.1129.

**IR (thin film):** 3361, 3287, 3094, 2958, 2929, 2871, 1746, 1691, 1656, 1567, 1514 cm\(^{-1}\).

**\(^1\)H NMR (CDCl\(_3\), 500 MHz):** \(\delta = 7.28–7.20 (m, 3 \ H), 7.09 (d, J = 7.3 \ Hz, 2 \ H), 6.40 (br s, 1 \ H), 5.05 (br s, 1 \ H), 4.85 (dd, (d, J = 5.0, 1.0 \ Hz, 1 \ H), 3.90 (m, 1 \ H), 3.68 (d, J = 1.4 \ Hz, 3 \ H), 3.10–3.07 (m, 2 \ H), 2.08–2.04 (m, 1 \ H), 1.43 (s, 9 \ H), 0.90 (d, J = 5.0 \ Hz, 3 \ H), 0.84 (d, J = 5.0 \ Hz, 3 \ H).**

**\(^13\)C NMR (CDCl\(_3\), 125 MHz):** \(\delta = 171.8, 171.3, 155.8, 135.8, 129.3, 128.7, 127.2, 79.9, 59.9, 53.23, 52.3, 38.0, 30.9, 28.4, 19.2, 17.7.**

**HRMS (ESI–TOF):** \(m/z\) [M + Na]\(^+\) calcd for C\(_{20}\)H\(_{30}\)N\(_2\)O\(_5\): 401.2052; found: 401.2052.

**Synthesis of Tripeptide 13**

TFA (1.00 mL) was added to a stirred solution of Boc-Val-Phe-OMe (0.22 g, 0.58 mmol) in anhydrous DCM (4 mL) at 0 °C and the mixture was stirred for 30 min. After completion of the reaction as observed in TLC, the solvent was removed under vacuum with addition of DCM (5 mL, 3 to 4 times). The residue (0.20 g, 0.58 mmol) was dissolved in anhydrous DCM (10 mL) in an ice bath, followed by addition of EDC·HCl·H\(_2\)O (0.22 g, 1.18 mmol) and HOBT (0.15 g, 1.18 mmol) and stirred for 20 min. Boc deprotected dipeptide \(12\) (0.22 g, 0.58 mmol) was added to the reaction mixture followed by DIPEA (0.20 mL, 1.30 mmol). The reaction mixture was stirred at r.t. for a further 6 h. On complete disappearance of starting material, the organic layer was washed with aqueous citric acid (3 × 15 mL) and 2 M aqueous NaHCO\(_3\) (3 × 15 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered, concentrated under vacuum, and purified by column chromatography.

**Methyl ((2S,3R)-3-((tert-Butoxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-l-valyl-l-phenylalaninate (13)**

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

Yield: 0.22 g (94%); white solid; \([M + Na]\(^+\) calcd for C\(_{25}\)H\(_{32}\)N\(_2\)O\(_6\): 536.3121; found: 536.3121.

**HRMS (ESI–TOF):** \(m/z\) [M + H]\(^+\) calcd for C\(_{25}\)H\(_{32}\)N\(_2\)O\(_6\): 536.3121; found: 536.3121.

**Asymmetric \(\alpha\)-Hydroxylation of Allylic 4**

L-Proline (0.13 g, 1.14 mmol, 30 mol%) and nitrosobenzene (0.44 g, 2.74 mmol) were added to a mixture of \(1\) (1.00 g, 3.80 mmol) in anhydrous DMSO (10 mL) at 15 °C and the mixture was stirred for 3 h at the same temperature. After 3 h the reaction was cooled to 0 °C and phosphorane Ph\(_3\)P=CO\(_2\)Et (2.65 g, 7.60 mmol) in DCM (10 mL) was added and the reaction mixture was stirred for a further 2 h at 0 °C. On complete disappearance of starting material, the reaction was quenched with saturated aqueous KHSO\(_4\) (10 mL) and the mixture was extracted with EtOAc (2 × 40 mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\), filtered, concentrated under vacuum, and purified by column chromatography.
Ethyl (4S,5S,R,E)-5-\{[(tert-Butoxycarbonyl)amino]-4-hydroxy-6-phenylhex-2-eneoate (15)
Column chromatography (petroleum ether/EtOAc, 80:20).
Yield: 0.80 g (70%); clear oil; [α]D27 –3.91 (c 0.23, CHCl3).
IR (thin film): 3355, 2926, 1729, 1683, 1524 cm–1.
1H NMR (CDCl3, 500 MHz): δ = 7.31–7.17 (m, 5 H), 6.98 (dd, J = 15.0, 5.0 Hz, 1 H), 6.15 (d, J = 15.0, 5.0 Hz, 1 H), 4.62 (dd, J = 10.0 Hz, 1 H), 4.43 (br s, 1 H), 4.21 (q, J = 5.0 Hz, 2 H), 4.02 (s, 1 H), 3.81 (s, 1 H), 2.84–2.77 (m, 2 H), 1.36 (s, 9 H), 1.29 (t, J = 5.0 Hz, 3 H).
13C NMR (CDCl3, 125 MHz): δ = 166.4, 157.0, 146.0, 137.4, 129.2, 128.8, 126.9, 122.8, 80.5, 73.6, 60.6, 57.0, 36.2, 29.8, 28.3, 14.3.

Procedure for Oxazolidine Protection of 15
A catalytic amount of p-TsOH (0.09 g, 0.57 mmol) and dimethoxypropane (1.11 mL, 8.59 mmol) were added to a stirred solution of diol (1.11 mL, 8.59 mmol) in DMSO (10 mL) at r.t. and the mixture was stirred for 3 h. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NaHCO3 (20 mL). The combined organic phases were dried over Na2SO4, filtered, concentrated under reduced pressure, and purified by column chromatography.
tert-Butyl (4R,5S)-4-Benzyl-2,2-dimethyl-5-(3-oxopropyl)oxazolidine-3-carboxylate (18)
Column chromatography (petroleum ether/EtOAc, 80:20).
Yield: 0.63 g (88%); clear oil; [α]D27 +15.25 (c 0.72, CHCl3).
IR (thin film): 2927, 2854, 2719, 1727, 1696, 1604 cm–1.
1H NMR (CDCl3, 500 MHz): δ = 9.60, 9.57 (s, 1 H), 7.30–7.15 (m, 5 H), 4.25–4.11 (m, 1 H), 3.99–3.96 (m, 1 H), 2.96–2.79 (m, 2 H), 2.44–2.29 (m, 1 H), 2.23–2.08 (m, 1 H), 1.95–1.79 (m, 1 H), 1.69–1.63 (m, 3 H), 1.54–1.50 (m, 4 H), 1.46–1.44 (m, 5 H), 1.35 (s, 4 H).
13C NMR (CDCl3, 100 MHz): δ = 152.8, 152.2, 151.6, 138.9, 129.4, 129.3, 128.4, 126.8, 126.3, 126.2, 92.9, 92.4, 80.1, 79.8, 76.4, 76.2, 60.8, 60.6, 40.7, 36.5, 35.9, 29.8, 28.5, 28.4, 28.1, 27.4, 25.0, 23.8, 22.1.
Oxidation of Primary Alcohols
IBX (0.69 g, 2.47 mmol) was added to a solution of diol (2 × 30 mL) in DMSO (10 mL) at r.t. and the mixture was stirred for 3 h. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NaHCO3 (50 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (30 mL) and dried over Na2SO4, filtered, concentrated under reduced pressure, and purified by column chromatography.
tert-Butyl (4R,5S)-4-Benzyl-2,2-dimethyl-5-(3-oxoproxy)oxazolidine-3-carboxylate (18)
Column chromatography (petroleum ether/EtOAc, 80:20).
Yield: 0.63 g (88%); clear oil; [α]D27 +15.25 (c 0.72, CHCl3).
IR (thin film): 2927, 2854, 2719, 1727, 1696, 1604 cm–1.
1H NMR (CDCl3, 500 MHz): δ = 9.60, 9.57 (s, 1 H), 7.30–7.15 (m, 5 H), 4.25–4.11 (m, 1 H), 3.99–3.96 (m, 1 H), 2.96–2.79 (m, 2 H), 2.44–2.29 (m, 1 H), 2.23–2.08 (m, 1 H), 1.95–1.79 (m, 1 H), 1.69–1.63 (m, 3 H), 1.54–1.50 (m, 4 H), 1.46–1.44 (m, 5 H), 1.35 (s, 4 H).
13C NMR (CDCl3, 100 MHz): δ = 152.8, 152.2, 151.6, 138.9, 129.4, 129.3, 128.4, 126.8, 126.3, 126.2, 92.9, 92.4, 80.1, 79.8, 76.4, 76.2, 60.8, 60.6, 40.7, 36.5, 35.9, 29.8, 28.5, 28.4, 28.1, 27.4, 25.0, 23.8, 22.1.
Synthesis of 20 from Diol 19
Na2O2 (0.56 g, 2.62 mmol) was added to a stirred solution of diol 19 (0.48 g, 1.31 mmol) in DCM/MegOH (1:1) and the mixture was filtered and the mixture was filtered and washed with brine (20 mL). The crude product was extracted with EtOAc (2 × 30 mL) and dried over Na2SO4, filtered, concentrated under reduced pressure, and purified by column chromatography.
tert-Butyl (4R,5S)-4-Benzyl-2,2-dimethyl-5-(2-oxoethyl)oxazolidine-3-carboxylate (20)
Column chromatography (petroleum ether/EtOAc, 80:20).
Yield: 0.38 g (85%); clear oil; [α]D27 –2.82 (c 0.49, CHCl3).
IR (thin film): 3439, 2975, 2931, 1727, 1697, 1495, 1455 cm–1.
1H NMR (CDCl3, 500 MHz): δ = 3.96, 3.94 (s, 1 H), 2.62–2.57 (m, 1 H), 2.52–2.46 (m, 1 H), 2.21–2.17 (m, 1 H), 1.39 (s, 15 H).
13C NMR (CDCl3, 100 MHz): δ = 200.0, 152.2, 151.7, 138.2, 137.3, 129.7, 129.4, 128.7, 126.9, 95.1, 94.4, 80.4, 74.3, 73.5, 63.3, 48.7, 48.2, 43.7, 39.8, 37.7, 29.8, 28.6, 26.9.
Synthesis of 21 from 20
Pyridinium dichromate (0.45 g, 1.20 mmol) was added to a stirred solution of 20 (0.10 g, 0.30 mmol) in DMF (10 mL) and stirring was continued at r.t. for 8 h. On complete disappearance of the starting material, the reaction was quenched with water (100 mL), the crude product was extracted with Et₂O (2 × 40 mL) and the combined organic phases were further extracted with saturated aqueous NaHCO₃ (2 × 30 mL). The aqueous extracts containing the carboxylate salt were combined and acidified with saturated aqueous KHSO₄ (2 × 40 mL) and extracted with Et₂O (2 × 50 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by column chromatography.

2-((4R,5S)-4-Benzyl-3-((tert-butoxycarbonyl)-2,2-dimethyloxazolidin-5-yl)acetic Acid (21)
Column chromatography (DCM/MeOH, 95:05).
Yield: 0.85 g (81%); clear oil; [α]D₂0 = –5.77 (c 0.48, CHCl₃).

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690223.

References and Notes
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