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-catalyzed 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-phenylalanine.

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 olivoreticulith 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 Various stereoselective methods 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.

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

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.10–12 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, we recently reported the synthesis of \( D\)-threo-sphinganine, \( L\)-erythro-sphinganine and \( L\)–spisulosine from an aldehyde derived from aspartic acid.

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

Scheme 1 Retrosynthetic analysis of compounds 1, 2 and 3 from 4

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

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

Scheme 2 Synthesis of bestatin (1a)

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

To synthesize phebestin, compound 9a was coupled with dipeptide 12, which was obtained from coupling the methyl ester of \( L\)-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).

β-Hydroxy-γ-amino acids have been designed for biologically active peptide mimics and for HIV protease inhibitors. Stictamide A, tasiamide B and hapolosin are biologically active peptide mimics and for HIV protease inhibitors.44–45 A variety of stereoselective methods for the synthesis of these acids and their analogues is available.46–50 (3R,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 (DMC) 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-

![Scheme 4 Synthesis of phebestin (2)](image_url)

![Scheme 5 Synthesis of 3 from aldehyde 4](image_url)
**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. TBDPSCI (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 at 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.

**tart-Butyl ((2R,3S)-3,4-Dihydroxy-1-phenylbutan-2-yl)carbamate (5a)**

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

Yield: 0.67 g (64%); clear oil; [α]D27 +8.59 (c 0.74, CHCl3).

IR (thin film): 3360, 2978, 2928, 1686, 1524 cm−1.

1H NMR (CDCl3, 500 MHz): δ = 7.31–7.22 (m, 5 H), 4.82 (d, J = 5.0 Hz, 1 H), 4.56 (d, J = 5.0 Hz, 1 H), 3.86–3.81 (m, 1 H), 3.68–3.36 (m, 4 H), 3.11–3.08 (m, 2 H), 2.92–2.88 (m, 2 H), 1.38 (s, 9 H).

13C NMR (CDCl3, 125 MHz): δ = 157.2, 137.4, 125.8, 125.7, 123.1, 129.4, 128.2, 120.9, 133.0, 72.8, 63.6, 59.4, 52.8, 39.6, 31.8, 28.3.


**tart-Butyl ((2R,3R)-3,4-Dihydroxy-1-phenylbutan-2-yl)carbamate (5b)**

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

Yield: 0.69 g (64%); clear oil; [α]D27 +11.94 (c 0.92, CHCl3).

IR (thin film): 3360, 2978, 2928, 1686, 1524 cm−1.

1H NMR (CDCl3, 500 MHz): δ = 7.27–7.18 (m, 5 H), 4.98 (d, J = 8.0 Hz, 1 H), 4.65 (d, J = 8.0 Hz, 1 H), 3.91–3.89 (m, 1 H), 3.63–3.38 (m, 4 H), 3.18 (br s, 1 H), 2.88 (d, J = 8.0 Hz, 2 H), 1.37 (s, 9 H).

13C NMR (CDCl3, 125 MHz): δ = 156.9, 138.0, 129.5, 129.3, 128.6, 126.5, 80.5, 80.1, 73.2, 71.6, 64.0, 59.6, 52.6, 38.2, 31.3, 29.8, 28.4.


**tart-Butyl (4R,5S)-4-Benzy1-5-((R)-2,3-dihydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (19)**

Column chromatography (petroleum ether/EtOAc, 60:50).

Yield: 0.68 g (65%); clear oil; [α]D27 +11.94 (c 0.92, CHCl3).

IR (thin film): 3418, 3063, 3029, 2924, 2855, 1694, 1682, 1604 cm−1.

1H NMR (CDCl3, 500 MHz): δ = 7.27–7.18 (m, 5 H), 4.29–4.10 (m, 2 H), 3.66 (br s, 1 H), 3.46–3.23 (m, 2 H), 2.97–2.82 (m, 2 H), 1.82–1.67 (m, 3 H), 1.57–1.53 (m, 6 H), 1.44, 1.34 (s, 9 H).

13C NMR (CDCl3, 125 MHz): δ = 151.9, 151.6, 138.7, 129.4, 129.3, 128.6, 128.4, 126.4, 126.2, 93.6, 92.9, 80.4, 80.0, 76.1, 71.2, 71.1, 66.3, 61.1, 60.9, 36.7, 36.0, 32.9, 28.4, 28.1, 27.5, 26.8, 25.2, 24.0.


**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.

**tart-Butyl ((2R,3R)-4-(((But-5-en-3-yl)oxy)-3-hydroxy-1-phenylbutan-2-yl)carbamate (6a)**

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

Yield: 0.84 g (78%); clear oil; [α]D27 +11.65 (c 0.48, CHCl3).

IR (thin film): 3298, 2856, 1715, 1494 cm−1.

1H NMR (CDCl3, 400 MHz): δ = 7.53–7.47 (m, 4 H), 7.35–7.15 (m, 11 H), 4.93 (d, J = 8.0 Hz, 1 H), 4.85–4.43 (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): δ = 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.

HRMS (ESI-TOF): m/z [M + H]+ calcd for C13H14NO4Si: 564.3145; found: 564.3141.

**tart-Butyl ((2R,3R)-4-(((But-5-en-3-yl)oxy)-3-(methoxy-methoxy)-1-phenylbutan-2-yl)carbamate (7a)**

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

Yield: 0.86 g (80%); clear oil; [α]D27 +11.05 (c 2.63, CHCl3).

IR (thin film): 3070, 3027, 2930, 2891, 2857, 1713, 1603, 1589 cm−1.
Yield: 0.52 g (90%); clear oil; \(\text{butan-2-yl)}\)carbamate (8b)

acidified with saturated aqueous KHSO\(_4\) (2 × 50 mL) and this was ex-
naqueous extracts containing the carboxylate salts were combined and
etched over Na\(_2\)SO\(_4\), filtered, concentrated under vacuum, and purified by column chromato-
graphy.

\(\text{tert-Butyl (2R,3S)-4-Hydroxy-3-(methoxymethoxy)-1-phenylbutano-2-yl)}\)carbamate (8a)

Column chromatography (petroleum ether/\(\text{EtOAc}\), 70:30).

Yield: 0.51 g (89%); clear oil; \([\alpha]_D^{27} +42.55\) (c 1.02, CHCl\(_3\)).

IR (thin film): 3334, 2924, 2853, 1715, 1497 cm\(^{-1}\).

1\(^{3}\)C NMR (CDCl\(_3\), 100 MHz):
\[\begin{array}{l}
129.4, 128.7, 128.6, 128.4, 128.4, 126.5, 115.5, 96.9, 79.2, 78.1, 67.2, 56.7, 53.3, 50.4, 41.5, 37.5, 29.8, 28.3, 24.9, 22.9, 21.8.
\end{array}\]

HRMS (ESI–TOF): \(m/z [M + H]^+\) calcd for \(\text{C}_{33}\text{H}_{46}\text{NO}_{5}\text{Si}: 564.3145\); found: 564.3149.

Silyl Deprotection; General Procedure

TBAF (1 M in THF, 1.94 mL, 1.94 mmol) was added to a stirred solution of compound \(7\) (1.00 g, 1.77 mmol) in anhydrous THF (15 mL) at \(0^\circ\) C and the solution was stirred at r.t. for 2 h. On complete disapearance of starting material, the reaction was quenched with satu-
rated aqueous NH\(_4\)Cl (30 mL) and the mixture was extracted with
\(\text{EtOAc (2} \times 30 \text{ mL})\). The combined organic phases were
dried over Na\(_2\)SO\(_4\), filtered, concentrated, and purified by column chromato-
graphy.

\(\text{tert-Butyl ((2R,3S)-4-Hydroxy-3-(methoxymethoxy)-1-phenylbutano-2-yl)}\)carbamate (8b)

Column chromatography (petroleum ether/\(\text{EtOAc}\), 70:30).

Yield: 0.24 g (82%); white solid; \([\alpha]_D^{27} +48.55\) (c 0.41, CHCl\(_3\)).

IR (thin film): 3395, 2924, 2853, 1692, 1603, 1497 cm\(^{-1}\).

1\(^{3}\)C NMR (CDCl\(_3\), 100 MHz):
\[\begin{array}{l}
128.7, 126.7, 96.8, 75.1, 56.7, 54.0, 38.5, 29.8, 28.3.
\end{array}\]

HRMS (ESI–TOF): \(m/z [M + Na]^+\) calcd for \(\text{C}_{17}\text{H}_{25}\text{NNaO}_{6}: 362.1580\); found: 362.1584.

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 addi-
tion 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 start-
ing material, the organic layer was washes with aqueous citric acid (3
\(\times 10\) mL) and 2 M aqueous NaHCO\(_3\) (3 \(\times 15\) mL). The organic layers were combined, dried
over Na\(_2\)SO\(_4\), filtered, concentrated, and purified by column chromato-
graphy.

Benzyl ((2S,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-L-leucinate (10a)

Column chromatography (petroleum ether/\(\text{EtOAc}\), 70:30).

Yield: 0.24 g (82%); white solid; \([\alpha]_D^{27} +32.23\) (c 0.69, CHCl\(_3\)); mp 99–101 °C.

IR (thin film): 3333, 3277, 3063, 3030, 2961, 2929, 2873, 1748, 1688, 1650, 1547, 1524 cm\(^{-1}\).

1\(^{H}\) NMR (CDCl\(_3\), 400 MHz): \(\delta = 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), 3.33 (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 = 4.3 Hz, 6 H).

1\(^{3}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta = 172.5, 170.5, 155.0, 137.8, 135.3, 129.4, 128.7, 128.6, 128.4, 128.4, 126.5, 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.

Oxidation of Primaries Alcohol; General Procedure

Pyridinium dichromate (11.56 g, 30.75 mmol) was added to the
stirred solution of alcohol \(8\) (1.00 g, 3.07 mmol) in DFM (30 mL) and
stirring was continued at r.t. for 8 h. On complete disappearance of the
starting material, the reaction was quenched with water (300 mL) and
extracted with \(\text{EtO}_2 (2 \times 50 \text{ mL})\). The combined organic phases were washed with
saturated aqueous NaHCO\(_3\) (2 \(\times 30 \text{ mL})\) and the aqueous extracts containing the carbonylate salts were combined and
acidified with saturated aqueous KHSO\(_4\) (2 \(\times 50 \text{ mL})\) and this was ex-
tracted with \(\text{EtO}_2 (2 \times 50 \text{ mL})\). The ether layers were combined, dried
over Na\(_2\)SO\(_4\), filtered, concentrated, and purified by column chromato-
graphy.

**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 4 h. On complete disappearance of starting material, solvent was removed under vacuum and the white residual solid was triturated 3 to 4 times with cold EtOAc (5 mL).

**((2R,3R)-3-((tert-Butoxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-l-leucine (1b)**
Column chromatography (petroleum ether/EtOAc, 70:30).

Yield: 0.24 g (82%); white solid; [α]27° +14.68 (c 0.68, CHCl3); mp 98–99 °C.

IR (thin film): 3394, 2926, 1739, 1651, 1454 cm–1.


**Procedure for Hydrogenolysis of 10**
To a stirred solution of 10 (0.13 g, 0.24 mmol) in anhydrous MeOH (10 mL), Pd/C (10 mol%) was added and the mixture was stirred vigorously for 3 h at r.t. under H2. On complete disappearance of starting material, the reaction mixture was filtered through a Celite® pad, solvent was removed under vacuum and the residue was purified by column chromatography.

**((2S,3R)-3-((tert-Butoxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-l-leucine (11a)**
Column chromatography (CH2Cl2/MeOH, 95:5).

Yield: 0.10 g (92%); clear oil; [α]27° +21.11 (c 0.36, CHCl3).

IR (thin film): 3333, 2925, 2854, 1718, 1524, 1454 cm–1.

1H NMR (CDCl3, 500 MHz): δ = 7.33–7.17 (m, 10 H), 6.87 (d, J = 5.0 Hz, 1 H), 5.22–5.13 (m, 3 H), 4.71–4.61 (m, 3 H), 3.44–3.43 (m, 4 H), 2.93–2.55 (m, 2 H), 1.73–1.56 (m, 3 H), 1.34 (s, 9 H), 0.93 (d, J = 5.0 Hz, 6 H).

13C NMR (CDCl3, 125 MHz): δ = 127.6, 169.9, 155.6, 138.0, 135.4, 129.5, 128.7, 128.5, 128.4, 126.4, 96.9, 79.3, 78.8, 67.3, 56.4, 54.1, 50.7, 40.8, 36.8, 29.8, 28.4, 25.1, 22.9, 21.8.


**((2S,3R)-3-((tert-Butoxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-l-leucine (11b)**
Column chromatography (DCM/MeOH, 95:5).

Yield: 0.10 g (92%); clear oil; [α]27° +25.37 (c 0.66, CHCl3).

IR (thin film): 3300, 2954, 2740, 1730, 1520 cm–1.

1H NMR (CDCl3, 400 MHz): δ = 7.25–7.10 (m, 5 H), 5.24 (br s, 1 H), 4.63 (m, 2 H), 4.31–4.14 (m, 2 H), 3.35 (s, 3 H), 2.94–2.73 (m, 2 H), 1.79–1.53 (m, 3 H), 1.24 (s, 9 H), 0.93–0.83 (m, 6 H).

13C NMR (CDCl3, 100 MHz): δ = 175.7, 175.4, 170.6, 169.6, 157.3, 155.8, 138.3, 137.9, 129.6, 129.4, 126.4, 96.6, 96.4, 81.1, 79.5, 79.0, 78.4, 55.8, 54.2, 50.7, 50.4, 41.2, 37.4, 36.7, 32.0, 29.8, 28.3, 28.0, 25.1, 23.1, 22.8, 21.7, 14.2.

HRMS (ESI–TOF): m/z [M + H]+ calcd for C_{14}H_{16}NO_{3}: 210.1130; found: 210.1129.

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

Boc-Val-OMe (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 EDCl-HCl (0.35 g, 1.84 mmol) and HOBT (0.24 g, 1.84 mmol) and the mixture was stirred for 20 min. HCl·N-H-Ph-O-Me (0.19 g, 0.92 mmol) was added to the reaction mixture followed by DPEA (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.

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

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

Yield: 0.31 g (90%); white solid: [α]_{D}^{23}+30.38 (c 0.88, CHCl_{3}); mp 101–103 °C.

IR (thin film): 3312, 3064, 3029, 2962, 2925, 2854, 1716, 1650, 1524 cm\(^{-1}\). 1H NMR (CDCl\(_3\), 500 MHz): δ = 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, J = 15.0, 5.0 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).

13C NMR (CDCl\(_3\), 125 MHz): δ = 173.1, 172.8, 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: 400.2252.

**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 EDCl-HCl (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 (0.35 mL, 2.03 mmol). The mixture was cooled in an ice bath followed by addition of 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 20 min. HCl·N-H-Ph-O-Me (0.19 g, 0.92 mmol) was added to the reaction mixture followed by DIPEA (0.35 mL, 2.03 mmol). The mixture was stirred for 1 h at the same temperature. After the disappearance of starting material as observed in TLC, the reaction was quenched with saturated aqueous KHSO_{4} (10 mL) and the free acid 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.

**Procedure for Hydrolysis of 13**

LiOH (0.030 g, 0.48 mmol) was added to a stirred solution of 13 (0.24 g, 0.40 mmol) in MeOH/H_{2}O (4:1, 10 mL) at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. After the disappearance of starting material as observed in TLC, the reaction was quenched with saturated aqueous KHSO_{4} (10 mL) and the free acid 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.

**Asymmetric α-Hydroxylation of Aldehyde 4**

L-Proline (0.13 g, 1.14 mmol, 30 mol%) and nitrosobenzene (0.44 g, 4.18 mmol) were added to a stirred solution of 4 (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=CHCO_{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 NH_{4}Cl (30 mL) and the mixture was extracted with DCM (2 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_{2}SO_{4}, filtered, and concentrated under vacuum. The crude aminohydroxylated 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 the above product (1.43 g, 3.84 mmol) in EtOH (10 mL) and the mixture stirred at r.t. for 6 h. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NH_{4}Cl (20 mL) and the mixture was extracted with DCM (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over Na_{2}SO_{4}, filtered, concentrated under vacuum, and purified by column chromatography.
Ethyl (4S,5S,6R,7E)-5-((tert-Butoxycarbonylamino)-4-hydroxy-6-phenylhex-2-enoate (15)

Column chromatography (petroleum ether/EtOAc, 80:20). Yield: 0.80 g (70%); clear oil; \([\text{IR}]_{\text{thin film}}=2978, 2930, 1723, 1701, 1604 \text{ cm}^{-1}\). IR (thin film): 3355, 2926, 1729, 1683, 1524 cm\(^{-1}\). HRMS (ESI–TOF): \([\text{M} + \text{Na}]^+\) calcd for C\(_{22}\)H\(_{31}\)NNaO\(_5\): 412.2100; found: 412.2105.

13C NMR (CDCl\(_3\), 100 MHz): \(\delta = 165.8, 151.9, 151.5, 141.7, 141.6, 138.2, 137.1, 130.0, 129.9, 128.4, 128.2, 126.3, 126.2, 122.6, 93.7, 93.0, 80.4, 80.1, 75.7, 75.5, 63.2, 61.7, 61.3, 60.6, 60.5, 37.4, 36.6, 28.6, 28.5, 28.0, 27.4, 20.7, 25.2, 24.0, 14.3, 14.2.


Procedure for Oxazolidine Protection of 15

A catalytic amount of p-TsOH (0.09 g, 0.57 mmol) and dimethylopropane (1.11 mL, 8.59 mmol) were added to a stirred solution of \(\text{IBX} (0.69 \text{ g}, 2.47 \text{ mmol})\) was added to a solution of \(\text{diol} (19)\) in anhydrous DCM (20 mL) at 0 °C and the mixture was stirred at r.t. for 8 h. On complete disappearance of starting material, the reaction mixture was filtered and washed with brine (20 mL). The crude product was extracted with DCM (2 × 30 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\), filtered, concentrated under reduced pressure, and purified by column chromatography.

**tert-Butyl (4R,5S)-4-Benzyl-5-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylate (18)**

Column chromatography (petroleum ether/EtOAc, 80:20). Yield: 0.63 g (88%); clear oil; \([\text{IR}]_{\text{thin film}}=2927, 2854, 2719, 1727, 1696, 1604 \text{ cm}^{-1}\). IR (thin film): 3355, 2926, 1729, 1683, 1524 cm\(^{-1}\). HRMS (ESI–TOF): \([\text{M} + \text{Na}]^+\) calcd for C\(_{20}\)H\(_{31}\)NNaO\(_4\): 370.1992; found: 370.1992.

**Synthesis of 20 from Diol 19**

NaO\(_4\) (0.56 g, 2.62 mmol) was added to a stirred solution of \(\text{diol} (19)\) (0.48 g, 1.31 mmol) in DCM/MeOH (1:1, 10 mL) and the mixture was stirred at r.t. for 8 h. On complete disappearance of starting material, the reaction mixture was filtered and washed with brine (20 mL). The crude product was extracted with EtOAc (2 × 30 mL) and dried over Na\(_2\)SO\(_4\), 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 (20)**

Column chromatography (petroleum ether/EtOAc, 80:20). Yield: 0.38 g (85%); clear oil; \([\text{IR}]_{\text{thin film}}=3439, 2975, 2931, 1728, 1697, 1495, 1455 \text{ cm}^{-1}\). HRMS (ESI–TOF): \([\text{M} + \text{Na}]^+\) calcd for C\(_{20}\)H\(_{31}\)NNaO\(_4\): 356.1838; found: 356.1841.
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 EtO (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)acetate Acid (21)

Column chromatography (DCM/MeOH, 95:05).

Yield: 0.07 g (67%); clear oil; [α]D20² = -5.77 (c 0.48, CHCl₃).

IR (thin film): 2928, 2856, 2718, 1727, 1696 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 7.29–7.25 (m, 2 H), 7.21–7.20 (m, 3 H), 4.66–4.34 (m, 1 H), 3.89–3.83 (m, 1 H), 3.26 (br s, 1 H), 2.88–2.66 (m, 1 H), 2.49–2.44 (m, 1 H), 2.23–2.19 (m, 1 H), 1.37 (s, 15 H).

13C NMR (CDCl₃, 100 MHz): δ = 175.6, 152.3, 138.2, 137.5, 129.4, 128.7, 126.9, 79.7, 47.7, 47.5, 40.8, 31.3, 29.8, 28.4.


Synthesis of Aldehyde 4

To a stirred solution of methoxymethyltriphenyl-phosphonium chloride (2.05 g, 6.02 mmol) and t-BuOK (0.58 g, 5.21 mmol) in anhydrous THF (10 mL), HN-Boc-Ø-phenyl-alaninal (1.00 g, 4.01 mmol) in anhydrous THF (10 mL) was added slowly at –10 °C and the mixture was stirred vigorously for 2 h at the same temperature. On complete disappearance of starting material, the reaction was quenched with saturated aqueous NaHCO₃ (30 mL) and the mixture was extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated under reduced pressure, and purified by column chromatography using 90:10 petroleum ether/EtOAc as eluent.

tert-Butyl (R)-(4-Oxo-1-phenylbutan-2-yl)carbamate (4)

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

Yield: 0.85 g (81%); clear oil; [α]D20² = +12.04 (c 0.51, CHCl₃).

IR (thin film): 2928, 2858, 2718, 1769, 1604 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 9.69 (s, 1 H), 7.31–7.14 (m, 5 H), 4.76 (br s, 1 H), 4.25 (br s, 1 H), 2.95–2.61 (m, 2 H), 2.58–2.48 (m, 2 H), 1.39 (s, 9 H).

13C NMR (CDCl₃, 100 MHz): δ = 175.5, 131.3, 130.2, 129.4, 128.7, 126.9, 79.7, 47.7, 47.5, 40.8, 31.3, 29.8, 28.4.


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Supporting Information

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