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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Key words asymmetric hydroxylation, organocatalysis, reductive cleavage

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-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 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.

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, we recently reported the synthesis of \( \text{d-threo-sphinganine} \), \( \text{l-erythro-sphinganine} \) and \( \text{(-)-spisulosine} \) 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.

Aldehyde 4 (for preparation see the literature) was subjected to diastereoselective hydroxylation using nitrosobenzene, and \( \text{d-proline} \) as catalyst and subsequently reduced to the corresponding primary alcohol by \( \text{NaBH}_4 \) in one pot. The crude product was further subjected to N–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, HOBt 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).

Epibestatin 1b was obtained in an overall yield of 22% from aldehyde 4 using exactly the same sequence of reactions but using \( \text{l-proline} \) 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 haploisin are biologically important compounds that contain 4-amino-3-hydroxy-5-phenylpentaonic acid as a structural fragment. The activities of such compounds depend on the stereochemistries of both the amino- and hydroxyl groups. A variety of stereoselective methods for the synthesis of these acids and their analogues is available. (3S,4R)-4-Amino-3-hydroxy-5-phenylpentaonic 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 (DMF) 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-phenylpentaonic 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 (15 mL) and the mixture was extracted with EtOAc (10 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; \([\delta]_{D}^{2}+11.94\) (c 0.92, CHCl₃).

IR (thin film): 3360, 2978, 2928, 2865, 1684, 1524 cm⁻¹.

**tert-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; \([\delta]_{D}^{2}+8.59\) (c 0.74, CHCl₃).

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

**tert-Butyl (4R,5S)-4-Benzyl-5-((R)-2,3-dihydroxypropyl)-2,2-di-methyloxazolidine-3-carboxylate (19)**

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

Yield: 0.68 g (65%); clear oil; \([\delta]_{D}^{2}+11.94\) (c 0.92, CHCl₃).

IR (thin film): 3318, 3063, 3029, 2924, 2855, 1694, 1682, 1604 cm⁻¹.

**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 ºC. TBDPSI (1.67 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.

**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; \([\delta]_{D}^{2}+17.28\) (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 = 155.5, 135.6, 133.1, 129.7, 128.6, 127.9, 127.0, 79.1, 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; \([\delta]_{D}^{2}+2.26\) (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, DIPA (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 ºC, 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; \([\delta]_{D}^{2}+1.65\) (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, 127.9, 127.0, 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 C₂₃H₂₄NO₆Si: 564.3145; found: 564.3141.

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

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

Yield: 0.86 g (80%); clear oil; \([\delta]_{D}^{2}+11.05\) (c 2.63, CHCl₃).

IR (thin film): 3070, 3027, 2930, 2891, 2857, 1713, 1603, 1589 cm⁻¹.
butan-2-yl)carbamate (8b) acidified with saturated aqueous KHSO4 (2 × 50 mL) and this was extracted. The aqueous extracts containing the carboxylate salts were combined and washed with saturated aqueous NaHCO3 (2 × 30 mL) and the organic layer was washed with EtOAc (2 × 30 mL). The combined organic phases were dried over Na2SO4, 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 7 (1.00 g, 1.77 mmol) in anhydrous THF (15 mL) at 0 °C and the solution was stirred at rt for 4 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 dried over Na2SO4, 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; [α]D27 +42.55 (c 0.79, CHCl3).

IR (thin film): 3333, 3277, 3063, 3030, 2962, 2929, 2873, 1748, 1688, 1625 cm−1.

1H NMR (CDCl3, 400 MHz): δ = 7.70–7.68 (m, 4 H), 7.45–7.38 (m, 6 H), 7.25–7.16 (m, 5 H), 5.38 (d, J = 12.0 Hz, 1 H), 4.65 (br s, 2 H), 4.17 (d, J = 8.0 Hz, 1 H), 3.84–3.80 (m, 1 H), 3.71–3.61 (m, 2 H), 3.32 (s, 3 H), 2.82 (d, J = 8.0 Hz, 2 H), 1.35 (s, 9 H), 1.08 (s, 9 H).

13C 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, 126.1, 96.6, 93.6, 78.7, 64.4, 63.5, 55.7, 52.9, 38.6, 36.9, 28.4, 26.9, 19.2.

HRMS (ESI−TOF): m/z [M + H]+ calcd for C17H24NO5Si: 564.3145; found: 564.3149.

Yield: 0.79 g (76%); clear oil; [α]D27 +49.18 (c 0.29, CHCl3).

IR (thin film): 3334, 2924, 2853, 1715, 1497 cm−1.

1H NMR (CDCl3, 500 MHz): δ = 8.03 (s, 1 H), 7.30–7.19 (m, 5 H), 5.09 (d, J = 8.0 Hz, 1 H), 4.77–4.70 (m, 2 H), 4.37 (d, J = 4.0 Hz, 1 H), 4.17 (s, 1 H), 3.46 (s, 3 H), 2.90–2.88 (m, 2 H), 1.34 (s, 9 H).

13C NMR (CDCl3, 125 MHz): δ = 173.1, 163.2, 155.6, 137.5, 129.4, 128.7, 126.7, 96.8, 80.1, 75.1, 56.7, 54.0, 38.5, 29.8, 28.3.


(2R,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoic Acid (9a)

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

Yield: 0.80 g (78%); clear oil; [α]D27 +48.55 (c 0.41, CHCl3).

IR (thin film): 3395, 2924, 2853, 1692, 1603, 1497 cm−1.

1H NMR (CDCl3, 400 MHz): δ = 7.30–7.19 (m, 5 H), 5.07 (d, J = 8.0 Hz, 1 H), 4.76–4.69 (m, 2 H), 4.37 (d, J = 8.0 Hz, 1 H), 4.16 (br s, 1 H), 3.45 (s, 3 H), 2.88 (d, J = 8.0 Hz, 2 H), 1.33 (s, 9 H).

13C NMR (CDCl3, 100 MHz): δ = 173.4, 163.4, 155.3, 137.5, 129.3, 128.3, 128.4, 96.6, 79.6, 56.2, 53.3, 36.9, 36.0, 31.8, 29.7, 28.2, 28.0.


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 rt 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 Na2SO4, filtered, concentrated, and purified by column chromatography.

Benzyl ((2S,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutan-2-yl)l-leucinate (10a)

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

Yield: 0.24 g (82%); white solid; [α]D27 +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 = 4.3 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, 126.3, 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.
**HRMS (ESI–TOF):** m/z [M + H]⁺ calcd for C₃₀H₄₃N₂O₇: 543.3070; found: 543.3079.

**Benzyl ((2R,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-L-leucine (10b)**

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

Yield: 0.24 g (82%); white solid; [α]D²⁷ +14.68 (c 0.68, CHCl₃); mp 98–99 °C.


**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 rt. under H₂. On complete disappearance of starting material, the mixture was filtered through a Celite® pad, solvent was removed under vacuum and the residue was purified by column chromatography.

**[(2S,3R)-3-((tert-Butyloxycarbonyl)amino)-2-(methoxymethoxy)-4-phenylbutanoyl)-L-leucine (11a)]**

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

Yield: 0.10 g (92%); clear oil; [α]D²⁷ +21.11 (c 0.36, CHCl₃).


**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 rt. 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).

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

Yield: 0.058 g (94%); white solid; [α]D²⁷ –15.83 (c 0.24, CH₂OH); mp 212–215 °C [lit.19 [α]D²⁰ –15.2 (c 0.83, 1 M HCl); mp 210–214 °C].


**[(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl)-L-leucine (1b)]**

Yield: 0.060 g (97%); white solid; [α]D²⁷ +5.82 (c 0.38, H₂O); mp 226–228 °C [lit.20 [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]D²⁷ –12.20 (c 1.02, H₂O); mp 187–189 °C [lit.19 [α]D²⁰ –11.9 (c 1.00, HAc); 188–191 °C].


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

Yield: 0.032 g (98%); clear oil; [α]D²⁷ –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·H2N-OMe·OMe (0.19 g, 0.92 mmol) was added to the reaction mixture followed by DIPA (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 NaHCO3 (3 × 15 mL). The organic layers were combined, dried over Na2SO4, filtered, concentrated under vacuum, and purified by column chromatography.

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

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

Yield: 0.24 g (70%); white solid; [1]D 27 +15.69 (c 0.86, CHCl 3); mp 101–103 °C.

IR (thin film): 3312, 3064, 3029, 2962, 2925, 2854, 1716, 1716, 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 = 171.8, 171.3, 155.8, 135.8, 129.3, 128.7, 127.2, 79.9, 59.9, 53.2, 52.3, 38.0, 30.9, 28.4, 19.2, 17.7.

HRMS (ESI–TOF): m/z [M + Na]+ calcd for C_{32}H_{46}N_{3}O_{8}: 600.3285; found: 600.3282.

**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/H2O (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 KHSO4 (10 mL) and the free acid was extracted with EtOAc (2 × 40 mL). The organic layers were combined, dried over Na2SO4, 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 Ph3P=CHCO2Et (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 NH4Cl (30 mL) and the mixture was extracted with DCM (2 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over Na2SO4, 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.

1H NMR (CDCl 3, 500 MHz): δ = 7.47 (br s, 1 H), 7.27–7.13 (m, 10 H), 6.07 (br s, 1 H), 5.07 (d, J = 5.0 Hz, 1 H), 4.81 (br s, 1 H), 4.61–4.59 (m, 2 H), 4.34–4.07 (m, 3 H), 3.39 (s, 3 H), 2.90–2.71 (m, 3 H), 2.04 (br s, 1 H), 1.76–1.61 (m, 1 H), 1.25 (s, 9 H), 0.89–0.84 (m, 6 H).

13C NMR (CDCl 3, 125 MHz): δ = 175.7, 174.2, 173.7, 171.0, 170.7, 156.6, 155.1, 137.9, 137.6, 136.1, 129.6, 128.6, 127.1, 126.7, 115.5, 97.3, 96.9, 81.1, 79.6, 78.5, 58.4, 58.2, 56.9, 55.7, 53.7, 39.7, 38.5, 37.8, 31.8, 31.1, 29.8, 28.3, 27.9, 20.8, 19.4, 18.3.

HRMS (ESI–TOF): m/z [M + H]+ calcd for C_{11}H_{14}N_{2}O_{4}: 586.3128; found: 586.3121.
Ethyl (4S,5S,6R,7S)-5-[(1R,2S,5S)-4-Benzyl-5-(3-hydroxypropyl)-2,2-dimethyl-oxazolidin-3-carboxylate (17)]

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

Yield: 0.72 g (80%); clear oil; [α]<sub>D</sub> +21.04 (c 0.51, CHCl<sub>3</sub>).

IR (thin film): 3445, 3062, 3027, 2928, 2856, 1696, 1604 cm<sup>–1</sup>.

1H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 7.29–7.14 (m, 5 H), 4.26–4.11 (m, 1 H), 4.05–3.86 (m, 1 H), 3.52–3.50 (m, 2 H), 3.22–3.18 (dd, J = 12.0, 4.0 Hz, 1 H), 2.92–2.81 (m, 2 H), 1.66–1.49 (m, 9 H), 1.43 (s, 4 H), 1.32 (s, 4 H), 1.24 (s, 2 H).

13C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 152.0, 151.7, 139.1, 139.1, 129.5, 129.3, 128.5, 128.3, 126.1, 93.0, 92.4, 80.1, 79.7, 62.4, 60.9, 60.8, 36.5, 35.9, 29.9, 28.5, 28.4, 28.1, 27.5, 26.2, 25.0, 23.8.

HRMS (ESI–TOF): m/z [M + Na]<sup>+</sup> calcd for C<sub>27</sub>H<sub>30</sub>NaO<sub>6</sub>: 536.1838; found: 536.1841.

Oxidation of Primary Alcohols

IBX (0.69 g, 2.47 mmol) was added to a solution of 17 (0.72 g, 2.06 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 NaHCO<sub>3</sub> (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 Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure, and purified by column chromatography.

tert-Butyl (4R,5S)-5-(3-Hydroxypropyl)-2,2-dimethyl-oxazolidine-3-carboxylate (18)

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

Yield: 0.63 g (88%); clear oil; [α]<sub>D</sub> +15.25 (c 0.72, CHCl<sub>3</sub>).

IR (thin film): 2927, 2854, 2719, 1727, 1696, 1604 cm<sup>–1</sup>.

1H NMR (CDCl<sub>3</sub>, 400 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 (CDCl<sub>3</sub>, 100 MHz): δ = 201.3, 152.0, 151.6, 138.9, 129.4, 129.3, 128.6, 128.4, 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

NaO<sub>2</sub> (0.56 g, 2.62 mmol) was added to a stirred solution of diol 19 (0.48 g, 1.31 mmol) in DCM/MeOH (1:1, 10 mL) and the mixture was stirred at r.t. for 3 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<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure, and purified by column chromatography.

tert-Butyl (4R,5S)-5-(2-Oxoyethyl)oxazolidine-3-carboxylate (20)

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

Yield: 0.38 g (85%); clear oil; [α]<sub>D</sub> +0.49 (c 0.49, CHCl<sub>3</sub>).

IR (thin film): 3439, 2975, 2931, 1728, 1697, 1495, 1455 cm<sup>–1</sup>.

1H NMR (CDCl<sub>3</sub>, 500 MHz): δ = 9.55 (s, 1 H), 7.30–7.19 (m, 5 H), 4.53–4.40 (m, 1 H), 3.84 (br s, 1 H), 3.32 (d, J = 5.0 Hz, 1 H), 2.76–2.71 (m, 1 H), 2.52–2.46 (m, 1 H), 2.21–2.17 (m, 1 H), 1.39 (s, 15 H).

13C NMR (CDCl<sub>3</sub>, 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.

HRMS (ESI–TOF): m/z [M + Na]<sup>+</sup> calcd for C<sub>26</sub>H<sub>28</sub>NaO<sub>4</sub>: 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 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)acetate (21)
Column chromatography (DCM/MeOH, 95:05).
Yield: 0.07 g (67%); clear oil; [α]D₂⁰ = −5.77 (c 0.48, CHCl₃).
IR (thin film): 2928, 2856, 2718, 1727, 1696, 1604 cm⁻¹.
1H NMR (CDCl₃, 400 MHz): δ = 7.29–7.25 (m, 2 H), 7.21–7.20 (m, 3 H), 4.46–4.34 (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, 97.9, 47.7, 47.5, 40.8, 31.3, 29.8, 28.4.

Funding Information
The author thanks CSIR for a Senior Research Fellowship.

Acknowledgment
The author thanks his Ph.D Thesis supervisor Dr. Ramesh Ramapicker for allowing him to work in his laboratory and for providing assistance, IIT Kanpur for providing instrumental facilities.

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

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