A short and enantioselective synthesis of N-terminal components of bestatin, amastatin and microginin

Prodeep Phukan
Department of Chemistry, Gauhati University, Guwahati 781014, India

Received 20 December 2000; accepted (revised) 17 October 2001

Synthesis of the N-terminal components of bestatin, amastatin and microginin has been achieved using Sharpless asymmetric amino hydroxylation reaction as key step.

In recent years, syn-α-hydroxy-β-amino acids have received considerable attention as the crucial component of many bioactive natural products. For example, bestatin Ia (2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl-S-leucine is well known as an immune-response modifier and inhibitor of aminopeptidase B. It is also found that, (2S, 3R)-α-hydroxy β-amino acid unit, is an important part of amastatin Ib and a marine natural product, microginin Ic which was recently isolated from the cultured fresh water blue-green algae Microcystis aeruginosa and exhibits inhibitory activity toward the angiotensin-converting enzyme (Figure 1). Therefore, construction of the α-hydroxy β-amino acid part is an important step towards the synthesis of these biologically active molecules. The importance of amino acids has prompted the development of a variety of methods, particularly their asymmetric synthesis.

Many methods have already been developed for the synthesis of α-hydroxy-β-amino acid units. Most of the early studies that used chiral natural products as starting materials were limited in their flexibility of structural modification. Although, more recently, several methods that are applicable to the synthesis of derivatives bearing a variety of side chains have been reported. Practical routes for the construction of both the enantiomers starting with common frameworks are still desirable. Recent discovery of asymmetric aminohydroxylation reaction by Sharpless opened a new dimension for the synthesis...
of chiral amino alcohols from olefins in one step. Herein, we wish to report a very concise synthesis of the N-terminal components of bestatin, amastatin and microginin applying Sharpless asymmetric aminohydroxylation procedure as key step.

Results and Discussion

The synthetic route for the synthesis of α-hydroxy-β-amino acids is depicted in Scheme 1. The olefins 2a-c were prepared by Wittig reaction of corresponding aldehyde with carbethoxymethyl triphenylphosphorane in benzene at reflux temperature. The olefin 2 was subjected to aminohydroxylation in the presence of DHQD-PHAL as chiral ligand to give the amino alcohols 3a-c. Hydrolysis of the esters 3 was done using K₂CO₃ in methanol to get the acids 1a-c. Optical purity was determined by comparing the optical rotations of the literature data.

In conclusion, a concise synthesis of (2S,3R)-3-amino-2-hydroxycarboxylic acids 1 is achieved successfully in good yield and optical purity (>95%) using Sharpless asymmetric aminohydroxylation process. The sequences of highly enantioselective aminohydroxylation and deprotection steps are quite practical for the synthesis α-hydroxy-β-amino acids.

Experimental Section

All solvents were distilled before use. Melting points are uncorrected. Compounds were purified by flash chromatography over silica gel (230-400 mesh). IR spectra were recorded on a Perkin Elmer 137 E Spectrometer and ¹H and ¹³C NMR spectra on a Bruker 200 MHz Instrument using TMS as internal standard. The optical rotations were determined using a JASCO – 181 digital polarimeter. The ligand DHQD – PHAL was procured from Aldrich, USA.

General procedure for the preparation of olefins

To a solution of carbethoxymethyltriphenylphosphorane (2.8g, 8.1 mmoles) in benzene (20mL), 1-octanal (1g, 7.8 mmoles) was added. The mixture was stirred at reflux for 2.5hr. The solvent was removed in vacuo and the residual oil extracted with pet-ether (3x20mL). The pet. ether solution was passed through a pad of silica gel and concentrated to get 1.4g light yellow oil.

Ethyl 3-(n-heptyl)acrylate 2a: Yield 90%; IR (Neat) cm⁻¹: 2895, 1700, 1635, 1440, 1250; ¹H NMR (200 MHz, CDCI₃): δ 0.9 (t, J=8.1Hz, 3H), 1.15-1.5 (m, 13H), 2.15 (q, J=8.1Hz, 2H, -CH₂CH₃), 4.15 (q, J=8.1Hz, 2H, -OCH₂); ¹³C NMR (50 MHz, CDCI₃): δ 13.69, 13.95, 22.40, 27.91, 28.93, 31.56, 31.92, 59.53, 121.19, 148.59, 165.91; Mass (m/z, % relative int.): 199 (M⁺, 4), 153(38), 127(17), 115(17), 110(32), 101(73); 81(50), 73(81), 69(63), 55(100).

Ethyl 3-(2-methylpropyl)acrylate 2b: Yield 92%; IR (Neat) cm⁻¹: 2900, 1705, 1635, 1445, 1255, 1160; ¹H NMR (200 MHz, CDCI₃): δ 0.9 (t, J=9.1Hz, 3H), 1.25 (t, J=7Hz, 3H, -CH₂CH₃), 1.65-1.85 (m, 1H) ; ¹³C NMR (50 MHz, CDCI₃): δ 13.13, 22.04, 27.91, 28.93, 31.56, 31.92, 59.53, 121.19, 148.59, 165.91; Mass (m/z, % relative int.): 199 (M⁺, 4), 153(38), 127(17), 115(17), 110(32), 101(73); 81(50), 73(81), 69(63), 55(100).

Ethyl 3-(2-methylpropyl)acrylate 2c: Yield 88%; IR (Neat) cm⁻¹: 2900, 1700, 1640, 1260; ¹H NMR (200 MHz, CDCI₃): δ 0.9 (d, J=6.4Hz, 3H, -CH₃), 1.3 (t, J=6.4Hz, 3H, -CH₂CH₃), 3.5 (dd, J=8.1Hz, 2H, -Ph-CH₂); 4.15 (q, J=8.1Hz, -OCH₂); 5.85 (d, J=15.7Hz, 1H), 6.9 (m, 1H); ¹³C NMR (50 MHz, CDCI₃): δ 14.6, 38.79, 60.56, 122.75, 126.66, 127.02, 129.05, 138.10, 147.61, 166.73.
General procedure for aminohydroxylation of olefins
To a stirred solution of DHQD-PHAL (0.098 g, 0.12 mmole, 5 mol %) in 15 mL of i-butanol and 15 mL of water was added. OsO4 (0.25 ml of 0.2 molar solution in toluene, 0.05 mmole, 2 mol %). After stirring for 2 min, chloramine-T trihydrate (1.72g, 7.6 mmoles, 3 mol equivalent) was added, followed by the olefin 2 (2.5 mmoles). The reaction was stirred till the green colour changed to yellow (about 2 hr). Ethyl acetate (15 mL) and sodium sulfite (1g) were added and stirred for 1 hr. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography using 10-15% ethyl acetate-pet ether.

(2S,3R)-Ethyl 2-hydroxy-3-(tosylamino)decanenoic acid 1a:
Yield 85%; m.p. 117.18°C; [α]D +28.4°(c, 1, acetone); 1H NMR (CDCl3): δ 8.0 (t, J=7Hz, 3H), 1.25 (t, J=7Hz, 3H), 1.5 (m, 1H), 1.75 (m, 1H), 2.45 (s, 3H), 3.35 (bs, 1H), 3.6 (m, 1H), 3.95-4.3 (m, 3H), 5.0 (d, J=10.8Hz, 1H), 7.3 (d, J=8.8Hz, 2H), 7.75 (d, J=8.4Hz, 2H); 13C NMR (CDCl3): δ 13.60, 20.96, 22.19, 25.46, 28.71, 31.28, 31.43, 32.03, 35.87, 61.76, 71.59, 126.71, 129.11, 138.52, 142.69, 172.66.

General procedure for hydrolysis of esters
To a solution of the ester 3 (1 mmole) in methanol (10 mL) was added K2CO3 (0.28g, 2 mmoles) in water (3 mL). The solution was stirred for 12 hr. Washed with ether and acidified with 2 N HCl to pH 2. The mixture was extracted with ether (3x10 mL) and the combined organic layer was washed with brine, dried over sodium sulfate and evaporated to give 1a-c.

(2S,3R)-2-Hydroxy-3-(tosylamino)decanonoic acid 1b:
Yield 93%; m.p. 141-143°C; [α]D +22.4°(c, 1, acetone); 1H NMR (CDCl3): δ 8.05 (t, J=3Hz, 3H), 0.9-1.3 (m, 12H), 2.35 (3H), 3.6 (bs, 1H), 4.2 (d, 1H), 5.6 (bs, 1H), 7.35 (d, J=5.4Hz, 2H), 7.75 (d, J=5.4Hz, 2H); 13C NMR (CDCl3): δ 14.42, 21.51, 23.32, 26.59, 29.84, 31.11, 32.21, 32.47, 37.13, 77.25, 127.93, 130.35, 140.54, 143.48, 206.81.

(2S,3R)-2-Hydroxy-5-methyl-3-(tosylamino)hexanoic acid 1c:
Yield 93%; m.p. 130-132°C; [α]D +32.4°(c, 1, acetone); 1H NMR (CDCl3): δ 8.0 (t, J=3Hz, 3H), 0.9-1.3 (m, 12H), 2.40 (3H), 3.7 (m, 1H), 4.20 (d, 1H), 5.0 (bs, 1H), 7.25 (d, J=5.4Hz, 2H), 7.7 (d, J=5.4Hz, 2H); 13C NMR (CDCl3): δ 20.22, 21.24, 23.73, 39.86, 53.89, 70.68, 129.2, 138.4, 143.2, 172.7.

Acknowledgement
This work was carried out at NCL with a fellowship from CSIR, New Delhi. The author acknowledges Dr A Sudalai for helpful guidance and laboratory facilities and CSIR, New Delhi for research fellowship.

References
1 (a) Suda H, Takita T, Aoyagi T & Umezaga H, Antibiotics, 26, 1976, 100.


