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Stereoselective Synthesis of [2S,3R]-β-Hydroxy Ornithine

B. Venkateswara Rao [a] , U. Murali Krishna [a] & Mukund K. Gurjar [a]
[a] Indian Institute of Chemical Technology , Hyderabad, 500007, India
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SYNTHETIC COMMUNICATIONS, 27(8), 1335-1345 (1997)

STEREOSELECTIVE SYNTHESIS OF [2S,3R]-ß - HYDROXY ORNITHINE

B. Venkateswara Rao, U. Murali Krishna and Mukund K. Gurjar*
Indian Institute of Chemical Technology, Hyderabad 500007, India

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Abstract: (2S,3R)-threo-ß-hydroxy ornithine has been synthesized in a stereoselective manner by the C_2 opening of epoxyalcohol **9** with benzyl isocyanate.

Proclavaminic acid **1** has recently been established as the biosynthetic precursor of clavulanic acid[1] **2**, a fused bicyclic ß-lactam which is a potent inhibitor of many bacterial ß-lactamases. Proclavaminic acid has been synthesised in three steps from *threo*-ß-hydroxy ornithine derivative[2] **3** which is also its biosynthetic precursor. ß-hydroxy ornithine is an useful building block and biogenetic precursor for various natural products. For example L-capreomycidine[3], an amino acid component of the antibiotic capreomycin was synthesized from **3**. Acivicin and 4-hydroxy acivicin[4] were also obtained biogenetically from ß-hydroxy ornithine. Although few syntheses[5] of this compound are known, only one synthesis is stereoselective and the rest require separation of diastereomers at appropriate stages.

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*To whom correspondence should be addressed.

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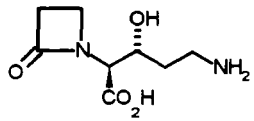
Herein we are presenting a highly stereoselective synthetic approach to (*2S,3R*)-ß-hydroxy ornithine.



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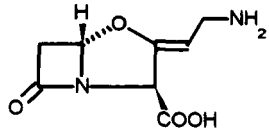

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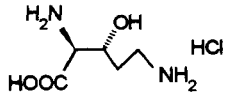

3

We initiated the synthesis of allylic alcohol **8** from the tetrahydropyranyl ether of propargyl alcohol **4**. Subsequent treatment of **4** with lithiumamide in liquid ammonia at -33°C followed by the addition of ethylene oxide furnished the alcohol **5** in 68% yield. At this juncture we decided to convert the triple bond of compound **5** into *cis*-double bond 6 by partial hydrogenation using P-II Nickel[6] as catalyst. The free hydroxyl group in **6** was protected as methoxyphenyl methyl (MPM) ether **7** by treatment with 1.2 eq. of sodium hydride and MPM bromide in dry THF at ambient temperature. In order to cleave the THP group, compound **7** was exposed to 5N HCl in methanol for 5 h to give the allylic alcohol **8**.

Sharpless asymmetric epoxidation[7] of **8** was performed in the presence of titanium tetraisopropoxide and 7M tert-butylhydroperoxide in isooctane and (+)-diisopropyl tartrate as a chiral auxiliary in CH_2Cl_2 at -20°C to furnish the epoxide **9** in 70% yield with 92% e.e. (HPLC on chiral cell OD). The C_2 directed ring opening[8] reaction was executed by treatment of **9** with benzyl isocyanate in the presence of triethylamine followed by reaction with sodium hydride in dry THF to

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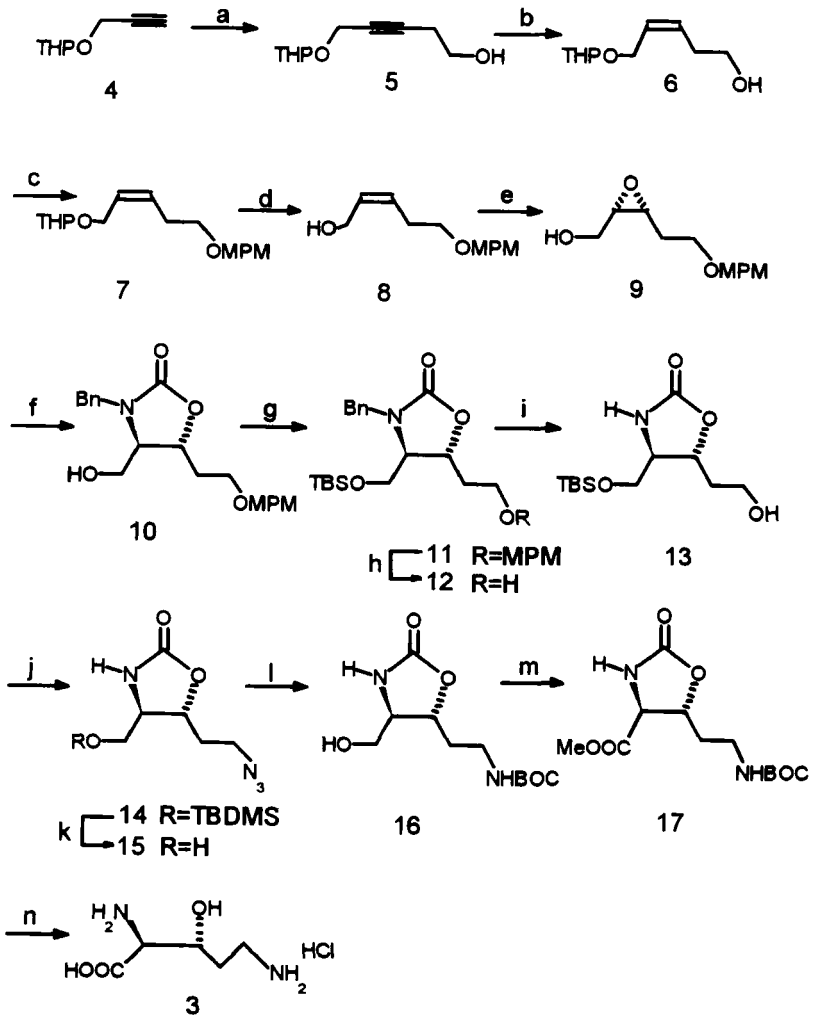

Reagents: a) $LiNH_2$, ethylene oxide, THF, -33°C, b) P-II Nickel, H_2, EtOH, c) NaH, MPMBr, THF, d) H+, MeOH, e) (+)-DIPT, TTIP, TBHP, Molecular seives, CH_2Cl_2, -20°C, f) BnNCO, Et3N, CH_2Cl_2, NaH, THF, g) TBDMS.Cl, Et_3N, CH_2Cl_2, h) DDQ, CH_2Cl_2-H_2O, i) Na/Liq.NH_3, j) MsCl, Et_3N, CH_2Cl_2, NaN_3, DMF, 90°C, k) H+, MeOH, l) Pd-C/H_2, EtOH; BOC_2O, Et_3N, m) Jone's reagent CH_2N_2, n) 6N HCl, reflux; NH_4OH.

afford 2-oxazolidinone derivative **10** in 72% yield. Reaction of **10** with TBS-Cl, imidazole in CH_2Cl_2 gave the TBS derivative **11** whose MPM group was removed by using DDQ to afford compound **12.** Hydrogenolysis of **12** with Na/liq.NH_3 at -33°C cleaved the benzyl group to obtain **13**. Transformation of **13** into azido derivative **14** via the corresponding mesylate was a straightforward exercise. After removing the TBS group by using 2N HCl in MeOH for 1 h **14** provided the alcohol **15.** Catalytic reduction of the azido group in **15** by using 10% Pd/C in EtOH at normal temperature and pressure followed by BOC protection gave the key intermediate **16** in 70% yield. The structure of **16** was supported by the ^{1}H-NMR, optical rotation ^{13}C-NMR, which were identical with the reported values[5e]. Compound **16** was converted into β-hydroxy ornithine hydrochloride by the known procedure. For example 16 was subjected to Jones oxidation, followed by esterification in the presence of diazomethane to give the ester **17**. In order to cleave the oxazolidinone ring, **17** was treated with 6N HCl to give ß-hydroxy ornithine hydrochloride whose spectral data and optical rotation were identical with the reported values.

In conslusion our synthesis gives *threo* ß-hydroxy ornithine in high optical purity and in overall good yields from cheaply available starting materials.

Experimental Section:

NMR spectra were recorded on varian Gemini (200 MHz) or varian unity 400 MHz spectrometer in $CDCl_3$. Tetramethylsilane was used as the internal standard. IR spectra were recorded on Shimadzu IR-470 spectrometer. Mass spectra were obtained by EI at 70 or 15 ev. with Finnigan Mat 1020B instrument. Optical rotations were measured on JASCO DIP 360 digital polarimeter, melting

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points were recorded on Mettler melting point apparatus or a Kofler hot plate and were uncorrected. All chromatographic separations were carried out using silica gel (100-200 mesh).

(Z)-5-(Tetrahydropyran-2-yloxy)-pent-3-en-1-ol (6)

To lithium amide [prepared from 1.12 g (160 mmol) lithium and 250 ml of liquid ammonia in the presence of catalytic amount of ferric nitrate] a solution of compound **4** (15.0 g, 107 mmol) in dry THF (30 ml) was added. After 1 h freshly distilled ethylene oxide (24.0 g, 537 mmol) was introduced over a period of 30 min. The reaction mixture was stirred for another 5 h, quenched with excess of solid NH_4Cl and partitioned between water and ethyl acetate. The organic layer was dried, concentrated and the residue was distilled at 113°C/0.1 mm of Hg to furnish pure **5** (13.3 g, 68%) as a syrup. ^{1}H-NMR : 4.72 (bs, 1 H), 4.15-4.25 (m, 2 H), 3.44-3.85 (m, 4 H), 2.3-2.5 (m, 2 H), 1.4-1.9 (m, 6 H).

To a freshly prepared suspension of P-II Nickel [prepared from nickel acetate pentahydrate (2.19 g) and sodium borohydride (0.34 g) in ethanol (15 ml)] was added ethylenediamine (1.17 ml) followed by compound **5** (13.0 g, 70 mmol) in ethanol (70 ml) and stirred vigorously under hydrogen atmosphere till the requisite amount of hydrogen (1585 ml) was absorbed. The reaction mixture was then filtered through celite bed and the residue washed with ethanol. The combined filtrates were concentrated and the residue partitioned between ethyl acetate and water. The organic layer was dried and concentrated to get **6** (10.5 g, 80%). ^{1}H-NMR : 5.5-5.8 (m, 2 H), 4.62 (bs, 1 H), 4.20 (dd, 1 H, J= 12.0 and 5.0 Hz), 4.05 (dd, 1 H, J= 12.0 and 7.0 Hz), 3.8 (m, 1 H), 3.61 (t, 2 H, J= 6.0 Hz), 3.45 (m, 1 H), 2.25-2.45 (m, 2 H), 1.4-1.9 (m, 6 H).

(Z)-5-(4-Methoxybenzyloxy)-pent-2-en-1-ol (8)

Compound **6** (10.0 g, 53.7 mmol) in THF (40 ml) was added to NaH (3.65

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g, 60% dispersion in mineral oil, 65 mmol) in THF (20 ml). After 1 h at room temperature MPM bromide 9.8 g (54.0 mmol) was added. The stirring was continued for 6 h and quenched with ice water. The reaction mixture was concentrated and then partitioned between ethyl acetate and water. The organic layer was concentrated and the residue was purified by column chromatography using ethyl acetate: hexane (1:9) as eluent to furnish **7** (12.5 g, 76%) as an oil. ^{1}H-NMR : 7.2 (d, 2 H, J= 8.4 Hz), 6.82 (d, 2 H, J= 8.4 Hz), 5.5-5.7 (m, 2 H), 4.6 (m, 1 H), 4.4 (s, 2 H), 4.05-4.3 (m, 2 H), 3.82 (m, 1 H), 3.78 (s, 3 H), 3.38 (m, 3 H), 2.3-2.45 (m, 2 H), 1.45-1.9 (m, 6 H).

Compound **7** (12.0 g, 39.0 mmol) 5N HCl (2 ml) in methanol (60 ml) were stirred at room temperature for 5 h and then worked-up. The residue was passed through a short silica gel column using ethyl acetate: hexane (1:4) as eluent to afford **8** (6.9 g, 80%). ^{1}H-NMR : 7.20 (d, 2 H, J= 8.5 Hz), 6.82 (d, 2 H, J= 8.5 Hz), 5.82 (m, 1 H), 5.58 (m, 1 H), 4.44 (s, 2 H), 4.04 (d, 2 H, J= 6.8 Hz), 3.77 (s, 3 H), 3.42 (t, 2 H, J= 6.0 Hz), 2.36 (dt, 2 H, J= 6.6 Hz). Analysis calculated for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.24

(2S,3R)-3-[2-(4-Methoxybenzyloxy)-ethyl]oxyranylmethanol (9)

To a stirred and cooled (-20°C) solution of (+) DIPT (0.37 ml, 1.76 mmol) and powdered molecular seives 4A° (6 g) in dry CH_2Cl_2 (10 ml) under N_2, titanium tetraisopropoxide (0.43 ml, 1.46 mmol) was added. After 15 min. a solution of allylic alcohol **8** (6.5 g, 29.2 mmol) in CH_2Cl_2 (30 ml) was introduced followed by after 20 min. with TBHP (9.4 ml, 7.0M solution in isooctane, 65.7 mmol). The reaction mixture was stored at -20°C for 48 h and worked-up as described in reference[7]. The residue was purified by column chromatography on silicagel with ethyl acetate: hexane (3:7) as eluent to give **9** (4.9 g, 70%). $[\alpha]_D$ +9.2 (c 1.0,

$CHCl_3$). ^{1}H-NMR : 7.2 (d, 2 H, J= 8.5 Hz), 6.82 (d, 2 H, J= 8.5 Hz), 4.42 (s, 2 H), 3.76 (s, 3 H), 3.3-3.7 (m, 4 H), 3.0 (m, 1 H), 2.95 (m, 1 H), 2.04 (m, 1 H), 1.70 (m, 1 H). Mass: m/z 238 (M+). The purity of the epoxide was confirmed by chiral HPLC on chiral OD by using 20% isopropanol/n-hexane as mobile phase and UV detection at 225 nm

(4R,5R)-3-benzyl-4-hydroxymethyl-5-[2-(4-methoxybenzyloxy)-ethyl]-oxazolidin--2-one (10)

To a solution of **9** (4.6 g, 19.3 mmol) in CH_2Cl_2 (40 ml) Et_3N (5.37 ml, 38.6 mmol) and freshly distilled benzyl isocyanate (3.1 ml, 25 mmol) was sequentially added. After being stirred overnight at room temperature, the reaction mixture was decomposed with saturated NH_4Cl and extracted with CH_2Cl_2 dried and concentrated. The crude product **9** (7.0 g) was dissolved in THF (100 ml) and then NaH (3.0 g, 60% dispersion in oil, 77.2 mmol) was added. After 5 h, the reaction was quenched by careful addition of sat. NH_4Cl and then extracted with CH_2Cl_2. The organic layer was dried concentrated and chromatographed on silica gel with ethyl acetate: hexane (1:1) as eluent to give **10** (5.1 g, 72%). $[\alpha]_D$ +43.4 (c 0.7, $CHCl_3$). ^{1}H-NMR : 7.25-7.45 (m, 5 H), 7.18 (d, 2 H, J= 8.5 Hz), 6.84 (d, 2 H, J= 8.5 Hz), 4.65 (d, 1 H, J= 15.5 Hz), 4.53 (m, 1 H), 4.35 (s, 2 H), 4.25 (d, 1 H, J= 15.5 Hz), 3.8 (s, 3 H), 3.4-3.7 (m, 4 H), 3.34 (m, 1 H), 1.8-1.95 (m, 2 H).

(4R,5R)-3-benzyl-5-(2-hydroxyethyl)-4-(tert.butyldimethyl-silyloxy)-methyl-oxazolidin-2-one (12)

To a solution of **10** (4.8 g, 13 mmol) TBS.Cl (2.32 g, 15.5 mmol) imidazole (1.77 g, 26 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for

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4 h and then worked up to give **11** (5.0 g, 80%). $[\alpha]_D$ +39.8 (c 1.1, $CHCl_3$). ^{1}H-NMR : 7.2-7.35 (m, 5 H), 7.13 (d, 2 H, J= 8.5 Hz), 6.79 (d, 2 H, J= 8.5 Hz), 4.75 (d, 1 H, J= 15.2 Hz), 4.39 (m, 1 H), 4.34 (s, 2 H), 4.08 (d, 1 H, J= 15.2 Hz), 3.77 (s, 3 H), 3.4-3.63 (m, 4 H), 3.26 (m, 1 H), 1.8 (m, 2 H), 0.86 (s, 9 H), 0.02 (s, 6 H).

Compound **11** (4.0 g, 8.2 mmol) DDQ (2.8 g, 12.3 mmol) in CH_2Cl_2: H_2O (35:5 ml) was stirred for 2 h at room temperature. The reaction mixture was washed successively with saturated sodiumbicarbonate solution, water, saturated NaCl, dried and concentrated the residue was purified by column chromatography using ethyl acetate: hexane (1:1) to give **12** (2.5 g, 85%). $[\alpha]_D$ +35.9 (c 0.8, $CHCl_3$). ^{1}H-NMR : 7.25-7.45 (m, 5 H), 4.83 (d, 1 H, J= 15.5 Hz), 4.51 (m, 1 H), 4.19 (d, 1 H, J= 15.5 Hz), 3.80 (m, 2 H), 3.64 (d, 2 H, J= 5.0 Hz), 3.38 (m, 1 H), 1.87 (m, 2 H), 0.9 (s, 9 H), 0.02 (s, 6 H). Analysis calculated for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55. Found: C, 62.27; H, 8.41

(4R,5R)-5-(2-Azidoethyl)-4-(tert.butyldimethylsilyloxy)-methyl-oxazolidin-2-one (14)

To liquid ammonia (50 ml) was added compound **12** (2.4 g, 6.5 mmol) in THF (10 ml) followed by sodium. After the blue colour persisted the reaction was stirred for 1 h. and quenched with solid NH_4Cl. Ammonia was evaporated and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was dried and concentrated to give **13** (1.53 g, 85%) as a white solid. m.p. 112°C; $[\alpha]_D$ +53.6 (c 0.8, $CHCl_3$). ^{1}H-NMR : 5.48 (brs, 1 H), 4.45 (m, 1 H), 3.8 (dd, 2 H, J= 6.0 Hz), 3.56 (m, 3 H), 1.8-2.0 (m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H). Mass: m/z 218 [M+-57 (t.butyl)].

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A solution of compound **13** (1.2 g, 4.36 mmol) Et_3N (1.2 ml, 8.72 mmol) methanesulfonyl chloride (0.5 ml, 6.54 mmol) and DMAP (50 mg) in CH_2Cl_2 (15 ml), was stirred at room temperature for 2 h. The reaction mixture was quenched with cold water, the organic layer was washed with saturated sodiumbicarbonate solution, water, dried and concentrated. The resulting mesylate and NaN_3 (1.4 g, 21.8 mmol) in dry DMF (10 ml) were heated at 90°C for 10 h. The reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and purified by column chromatography with ethyl acetate: hexane (2:3) as eluent to give **14** (0.9 g, 68%) as an oil. $[\alpha]_D$ +60.1 (c 1.0, $CHCl_3$); IR (Neat), max (cm^{-1}): 3395, 2920, 2090, 1730, 1250; ^{1}H-NMR (400 MHz): 5.76 (bs, 1 H), 4.40 (m, 1 H), 3.4-3.7 (m, 5 H), 2.10 (m, 1 H), 1.90 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 6 H). HRMS= m/z M^+ (300) - 57 (t-butyl); Found: 243.0909 cal. for $C_8H_{15}N_4O_3Si$ 243.0913

Tert-butyl(4R,5R)-2-(4-hydroxymethyl-2-oxa-oxazolidin-5-yl)ethyl-carbamate (16)

Compound **14** (0.8 g, 2.6 mmol), 2N HCl (0.2 ml) and MeOH (10 ml) were stirred at room temperature for 1 h. The solvent was evaporated, the residue dissolved in ethyl acetate, washed with water dried and concentrated. The residue was purified by column chromatography on silicagel using with ethyl acetate: hexane (9:1) as eluent to afford **15** (0.37 g, 75%) as a off white solid. m.p.- 64°C $[\alpha]_D$ 126.6 (c 1.0, $CHCl_3$). ^{1}H-NMR (400 MHz): 7.14 (bs, 1 H), 4.42 (m, 1 H), 3.4-3.6 (m, 5 H), 1.8-2.0 (m, 2 H). Mass : m/z (M^+ -31) : 155

Compound **15** (0.3 g, 1.6 mmol) was hydrogenated over 10% Pd/C (25 mg) in EtOH (8 ml) at atmospheric pressure for 12 h. The mixture was filtered through celite and concentrated. To the oily residue in DMF (4 ml) were added

Et_3N (0.27 ml) and di.tert..butyldicarbonate (0.42 g) and the reaction mixture was stirred for 12 h at room temperature and worked-up to give **16** (0.29 g, 70%). m.p. 102°C; $[\alpha]_D$ +55.3 (c 1.82, MeOH), lit.[5e] $[\alpha]_D$ +58.5 (c 2.3.8, MeOH). ^{1}H-NMR : 6.35 (bs, 1 H), 5.0 (bs, 1 H), 4.45 (q, 1 H, J= 6.5 Hz), 3.5-3.8 (m, 3 H), 3.2-3.4 (m, 2 H), 1.8-2.0 (m, 2 H), 1.45 (s, 9 H). ^{13}C NMR (50 MHz): 159.84, 156.38, 79.57, 77.34, 63.16, 59.25, 36.6, 35.11, 28.39. CIMS : m/z (M+ 1) : 261

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