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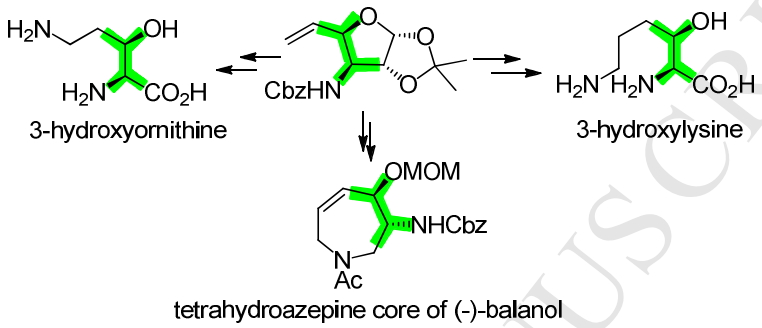

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ABSTRACT

D-Glucose derived synthon **4** was successfully utilized for the synthesis of (2*S*,3*R*)–*β*–hydroxyornithine **1**, (2*S*,3*R*)–*β*–hydroxylysine **2** and tetrahydroazepine core of balanol **3**.

1. Introduction

The non-proteinogenic *β*–hydroxy amino acids are important building blocks in the biosynthesis of peptides, protein scaffolds and antibiotics[1] as well as in the synthesis of complex natural products.[2] For example, *threo*-3-hydroxy-L-ornithine **1** (Figure 1) is an intermediate for the synthesis of the tuberculostatic cyclic peptide antibiotic capreomycidine as well as a biosynthetic precursor for *β*–lactamase inhibitor proclavaminic acid, clavulanic acid and anticancer agent acivicin.[3] One carbon homologated analogue of **1** is 3-hydroxylysine **2** which is a crucial marker in the oxidation of proteins.[4] Glycosylated derivatives of 5-hydroxylysine were found to be immunodominant T cell Epitope in murine of Type II collagen-the main protein part of articular cartilage associated with rheumatoid arthritis.[5] Moreover 3-hydroxylysine **2** is used as a synthetic intermediate for fungal metabolite balanol **3** which is an effective inhibitor of human protein kinase C (PKC)[6,7] in cellular signal transduction.[8] The PKC enzyme is also involved in the progression of diseases such as cardiovascular dysfunction, asthma, cancer, inflammation, central nervous system disorders, diabetic complications as well as HIV infection.[9] Thus, high selectivity and potency of balanol **3** towards the protein kinase enzymes renders it as an attractive target for new therapeutic agents.[10] The structural framework of balanol **3** contains the central chiral hexahydroazepine core that contains *β*–hydroxyl amine functionality in which the stereochemistry at carbons carrying amino and hydroxyl groups is exactly matching to that of carbons having amino-hydroxyl functionality in **1** and **2**.

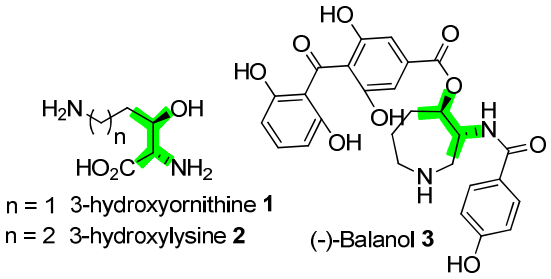
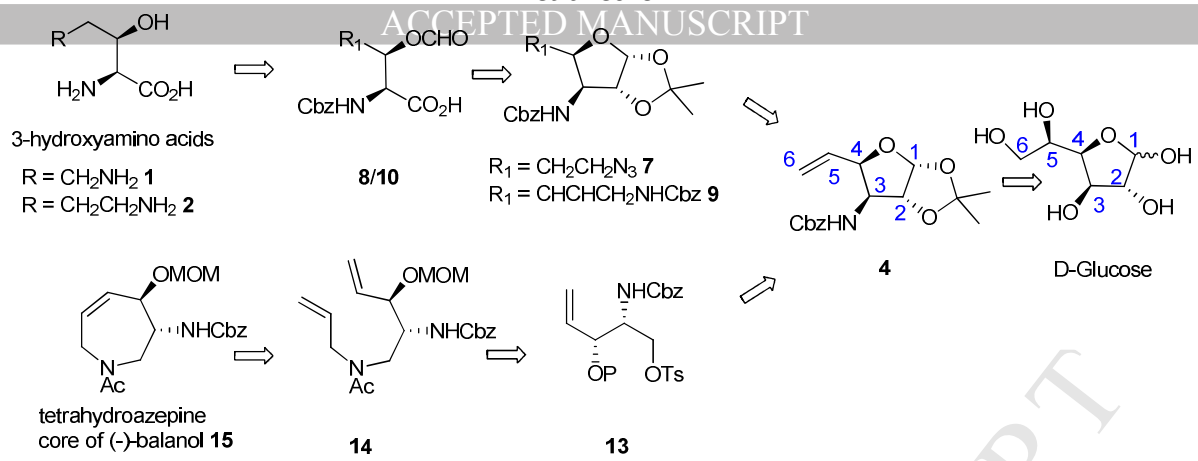


Figure 1: *β*–Hydroxy–*α*–amino acids **1**, **2** and (–)–balanol **3**.

The synthetic approaches to **1**, **2** and **3** involve both asymmetric as well as chiron approaches. The asymmetric pathways to **1** are based on the Sharpless asymmetric epoxidation,[11a] dihydroxylation[11b] and asymmetric aldol reaction.[12a] While chiron approaches make use of amino acids such as vinyl glycinate and D-serine.[12b-d] Also, the methods for the synthesis of **2** are reported in literature.[6,7,13] The synthesis of balanol **3** is focused on the synthesis of hexahydroazepine core[14] wherein the main challenge is to obtain required *β*–hydroxyamino functionality with defined absolute stereochemistry. Amongst the reported total synthesis of (–)–balanol **3**, asymmetric methods are based on (i) resolutions of the racemic mixtures[15a-g] or dynamic kinetic resolutions of allylic alcohols,[15h] desymmetrization reactions[15i,j] (ii) asymmetric epoxidation of unsaturated esters as well as allylic alcohols,[16a-c] aminohydroxylation of unsaturated aryl esters.[16d] (iii) asymmetric aziridination[15i] (iv) intramolecular stereo selective addition of sulfonium ylide to *N*-*t*butylsulfinyl imine.[16e]



Scheme 1: Retrosynthetic analysis of **1**, **2** and **3**.

In addition, some reports for the synthesis of **3** have been based on the chiral templates i.e D-serine [16f-k] and L-ascorbic acid.[16l]

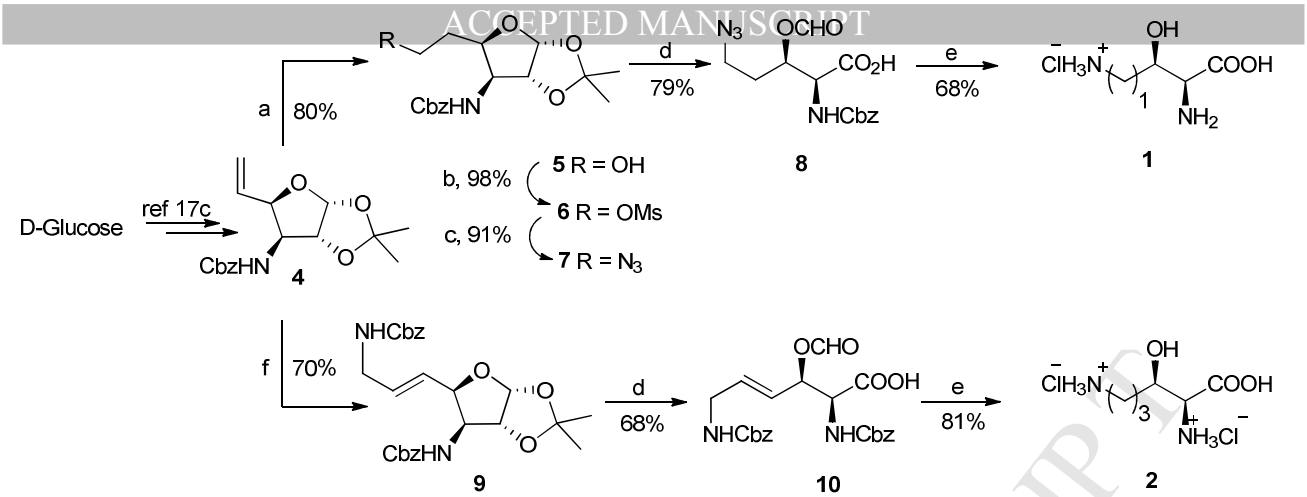
As a part of our continuous interest in the synthesis of chiral amino acids[17] and iminosugars,[18] we now report hitherto unknown and an efficient chiron approach for the synthesis of 3–hydroxyornithine **1**, 3-hydroxylysine **2** and tetrahydroazepine core of balanol **3** using the common precursor **4** obtained from D-glucose.

Results and discussion: As shown in the retrosynthetic analysis (Scheme 1), we visualized D-glucose type of hidden symmetry in the target molecules. The acid functionality of the target molecules **1** and **2** could be obtained by excision of the anomeric carbon in compound **7** followed by oxidation. The α-amino functionality of **1** and **2** could be derived from the double inversion of C3-hydroxy group of D-glucose and in case of **1** and **2** the terminal amino functionality could be derived by functionalization of C5-C6 carbon-carbon double bond in **4**. For balanol **3**, the functionalized azepine core could be accessed through ring closing metathesis (RCM) of acyclic diene precursor **14** (Scheme 1) that could be obtained by S_N2 displacement of tosyloxy group in **13** with allylamine. The 1,2 acetonide functionality in **4** could be manipulated to get **13**. Absolute configurations of C3 and C4 in **4** are identical with that of target molecules **1**, **2** and **3** justifying its use as common synthon.

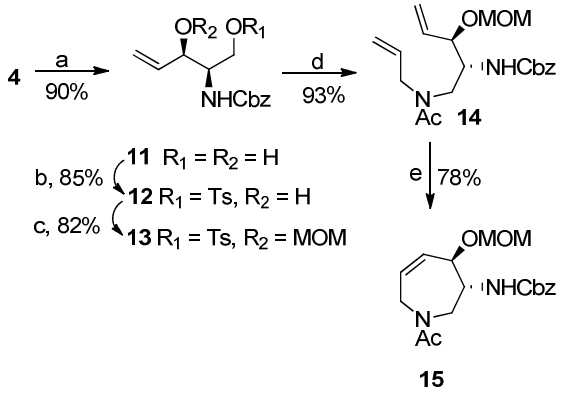
Synthesis of 1 and 2: The requisite 3-benzylcarbamate-3,5,6-trideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hexofuran-5-ene **4** was prepared according to the earlier report from our laboratory in 79% yield from D-glucose[17b] (Scheme 2). Hydroboration with B_2H_6 (*in situ* generated from $NaBH_4/I_2$) followed by oxidation (H_2O_2, NaOH) of sugar olefin **4** gave primary alcohol **5** in 80% yield.[19] In the next step, the primary alcohol is converted into *O*-mesyl derivative **6** (MsCl/TEA) and subsequently reacted with NaN_3 in DMF to get 6-azido-sugar derivative **7**. Deprotection of 1,2-acetonide functionality in **7** with TFA-water (9:1) afforded an anomeric mixture of hemiacetal that on oxidative cleavage using sodium metaperiodate in acetone–water followed by the Pinnick oxidation ($NaClO_2$, NaH_2PO_4) provided acid **8** as a viscous oil.[20] Finally, one pot reduction of azide functionality and deprotection of –*N*Cbz as well as removal of -*O*-formyl group using 10% Pd/C in MeOH-HCl afforded mono-hydrochloride salt of (2*S*,3*R*)-β-hydroxyornithine **1** as a solid in 68% yield. The spectral and analytical data of **1** was found to be in consonance with that reported {[mp 194-195 °C (lit.[12d] mp 123 °C)]; $[\alpha]_D^{28}$ +3.2 (*c* 2.9, H_2O) [lit.[12d] $[\alpha]_D^{25}$ +2.9 (*c* 3.0, H_2O)]}. For the synthesis of 3-hydroxylysine **2**, the sugar olefin **4** was subjected for the cross metathesis reaction using the -*N*Cbz protected allylamine in the presence of Grubb's second generation catalyst that afforded diamino sugar olefin derivative **9** in 70% yield. In the next step, treatment of **9** with TFA: H_2O (9:1) afforded an anomeric mixture of hemiacetal that was treated with $NaIO_4$ in acetone: H_2O (to get C2 aldehyde) followed by the Pinnick oxidation to get acid **10** in 68% yield over three steps. In the final step, deprotection of both the -*N*Cbz functionalities,-*O*-formyl group and reduction of the carbon-carbon double bond in one pot using catalytic 10% Pd/C provided bishydrochloride salt of **2** in 81% yield. The spectral and analytical data of **2** was found to be identical with that of reported {mp 190-191 °C, [reported[6a] 188–192 °C]; $[\alpha]_D^{28}$ +15.8, (*c* 1.88, CH_3OH), reported[6a] $[\alpha]_D^{25}$ +16.90, (*c* 1.83, CH_3OH)}.

Synthesis of tetrahydroazepine core of 3: For the synthesis of protected tetrahydoazepine core of balanol **3**, sugar olefin **4** was treated with TFA: H_2O (9:1) to get hemiacetal that on reaction with $NaIO_4$ followed by reduction of *in situ* generated C-2 aldehyde with $NaBH_4$ afforded 1,3 diol **11**. The primary hydroxyl group in diol **11** was selectively converted into tosyloxy derivative by treatment with TsCl in TEA using cat. amount of nBu$_2$SnO to get tosyl derivative **12** in 85% yield. In the next step, free allylic hydroxyl group in **12** was protected as a MOM ether using MOM chloride in the presence of DIPEA in dichloromethane under reflux condition to get **13** in 82% yield. Further, the S_N2 displacement of the tosyloxy group in **13** with allylamine in methanol at 60 °C followed by reaction with Ac_2O in pyridine afforded *N*-acetyl protected divinyl derivative **14.** In the final step, ring closing metathesis (RCM) of **14** using the Grubbs second-generation catalyst in dichloromethane at reflux conditions afforded the tetrahydroazepine core **15** that could be utilized for the synthesis of balanol **3** and its analogues (Scheme 3).

In summary, we have demonstrated the judicious manipulation of hydroxyl functionalities in D-glucose derived common synthon **4** for the synthesis of (2*S*,3*R*)-β-hydroxyornithine **1**, (2*S*,3*R*)-β-hydroxylysine **2** and tetrahydroazepine core of balanol **3**. The use of easily available reagents, mild reaction conditions and high yielding steps make our approach practicable for the synthesis of target molecules.



Scheme 2: Synthesis of **1** and **2**. Reagents and conditions: (a) $NaBH_4$, I_2, $NaOH/H_2O_2$; (b) MsCl, Et_3N, DCM; (c) NaN_3, DMF; (d) i. TFA/H_2O; ii. $NaIO_4$; iii. $NaClO_2$, H_2O_2; (e) H_2, Pd/C, MeOH:HCl (4:1); (f) *N*Cbzallyl amine, Grubbs IInd (10 mol %), DCM.



Scheme 3: Synthesis of **15**. Reagents and conditions: (a) i.TFA:H_2O (9:1); ii. $NaIO_4$, CH_3COCH_3: H_2O; iii. $NaBH_4$, THF: H_2O (4:1); (b) TsCl, nBu$_2$SnO, TEA, DCM; (c) MOMCl, DIPEA, DCM, reflux; (d) i. allyl amine, MeOH, 60 ^oC; ii. Ac_2O, Py, DCM; (e) Grubb's IInd, DCM, reflux.

Experimental section

General experimental methods:

All reactions were carried out with distilled and dried solvents using oven-dried glassware. Specialized reagents were purchased from commercial sources (Aldrich or fluka). ^{1}H NMR (300MHz/400MHz/500MHz) and ^{13}C NMR (75MHz/100MHz/125MHz) were recorded in $CDCl_3$ and D_2O as solvents. Chemical shifts were reported in δ unit (parts per million) with reference to TMS as an internal standard (In case of D_2O, HDO peak at δ 4.86). IR spectra were obtained using FTIR spectrophotometer as a thin film or using KBr pellets and recorded in cm^{-1}. High-resolution mass spectra were obtained with a HRMS Thermo-scientific Bruker Daltonic GmbH Germany Impact II UHR-TOF mass spectrometer ESI. Melting points were recorded using Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were measured on a digital polarimeter with sodium light (589.3 nm) at 24–30 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F254). Column chromatography was carried out with silica gel (100-200 mesh). After neutralization workup involves washing of combined organic layer with water, brine, drying over anhydrous sodium sulphate and evaporation of solvent under reduced pressure.

1,2-*O*-isopropylidene-3-(*N*-benzyoxycarbonyl)-amino- 3,5-dideoxy-α-D-*gluco*-1,4-furanose (5): To a stirred suspension of $NaBH_4$ (0.26 g, 6.9 mmol) in dry THF (25 mL) was added iodine (0.87 g, 3.44 mmol) in dry THF (15 ml) under nitrogen atmosphere over a period of 1 h at 0 ^oC. To this cooled solution was added solution of **4** (2.2 g, 15 mmol) in THF (10 mL) and the reaction mixture was stirred at 25 ^oC. After 3 h, reaction mixture was cooled to 0 ^oC and 3N NaOH (30 mL) and 30% H_2O_2 (30 mL) were added slowly and stirred for 20 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL × 3). The combined organic extract was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by silica gel column chromatography using (pet. ether/ EtOAc = 7/3) afforded alcohol **5** (1.85 g, 80%) as a thick liquid; R_f = 0.5 (30% EtOAc/pet. ether); $[\alpha]_D^{20}$ –14.8 (*c* 0.4, $CHCl_3$); IR (neat) ν max: 3200–3600 (br), 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.20 (5H, m, Ar-H), 5.80 (1H, d, *J* = 3.8 Hz, H-1), 5.13 (2H, AB quartet, *J* = 12.0 Hz, *O*-CH_2Ph), 4.88-4.72 (2H, br m, NH, D_2O), 4.53 (1H, d, *J* = 3.8 Hz, H-2), 4.44- 4.32 (1H, m, H-4), 4.20 (1H, d, *J* = 3.0 Hz, H-3), 3.86-3.69 (2H, m, H-6), 1.92-1.72 (2H, m, H-5), 1.53 (3H, s, -CH_3), 1.30 (3H, s, -CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 136.0, 130.9, 128.5, 128.3, 111.9, 26.0, 103.9, 84.5, 67.2, 60.0, 58.2, 30.8, 29.7, 26.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{17}H_{23}NO_6Na$, 360.1425; found 360.1424.

1,2-*O*-isopropylidene-3-(*N*-benzyoxycarbonyl)-amino-3,5-dideoxy-6-*O*-mesyl-α-D-*gluco*-1,4-furanose (6): To an ice cooled solution of alcohol **5** (2 g, 5.93 mmol) in dichloromethane (15 mL) was added triethylamine (2.5 mL, 17.78 mmol) and DMAP (0.01 g) followed by methanesulphonyl chloride (0.56 mL, 7.11 mmol) in dichloromethane (10 mL) over a period of 10 min and the resultant reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched by adding water (20 mL) and organic layer was separated. Usual work up and purification by column chromatography using pet. ether/ EtOAc = 8/2 gave **6** (2.4 g, 98%) as a thick liquid; R_f = 0.7 (30% EtOAc/pet. ether); $[\alpha]_D^{20}$ –8.7 (*c* 0.75, $CHCl_3$); IR (neat) ν max: 1710, 1440, 1350, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.20 (5H, br. m, Ar-H), 5.71 (1H, d, *J* = 3.8 Hz, H-1), 5.04 (2H, AB quartet, *J* = 12.5 Hz, *O*-CH_2Ph), 4.92-4.82

(1H, br,-*N*H), 4.43 (1H, d, *J* = 3.8 Hz, H-2), 4.33-4.10 (4H, m, H-6, H-3, H-4), 2.92 (3H, s, -*O*Ms), 2.01-1.84 (2H, m, H-5), 1.43 (3H, s, -CH_3), 1.22 (3H, s, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 155.7, 135.9, 130.9, 128.8, 128.6, 128.4, 128.2, 112.0, 103.7, 84.6, 74.7, 67.2 , 66.8, 57.9, 37.2, 28.3, 26.3, 26.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{25}NO_8SNa$ 438.1200; found 438.1199.

1,2-*O*-isopropylidene-3-(*N*-benzyoxycarbonyl)-amino-3,5-trideoxy-6-azido-α-D-*gluco*-1,4-furanose (7): To a stirred solution of **6** (2 g, 4.81 mmol) in DMF (10 mL) was added sodium azide (0.63 g, 9.63 mmol) and the reaction mixture was refluxed. After 1 h the solution was cooled to 25 °C, DMF was removed on rotary evaporator and the crude mixture was dissolved into EtOAc/H_2O (40 mL, 1:1). The organic layer was separated and aqueous phase was extracted with ethyl acetate (3×10 mL). Usual workup and column purification (pet. ether/ EtOAc = 9/1) afforded **7** (1.6 g, 91%) as a thick liquid; R_f = 0.54 (10% EtOAc/pet. ether); $[\alpha]_D^{28}$ −13.4 (*c* 0.11, $CHCl_3$); IR (neat) ν max: 2160, 1680, 1456, 1377 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.01 (5H, m, Ar-H), 5.75 (1H, d, *J* = 3.7 Hz), 5.08 (2H, AB quartet, *J* = 12.1 Hz), 4.99 (1H, d, *J* = 9.6 Hz), 4.47 (1H, d, *J* = 3.1 Hz), 4.29–4.21 (1H, m), 4.21–4.13 (1H, m), 3.38 (2H, t, *J* = 9.6 Hz), 1.88 –1.70 (2H, m), 1.49 (3H, s), 1.26 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 135.9, 128.5, 128.3, 128.1, 111.9, 103.7, 84.5, 75.6, 67.1, 57.8, 48.2, 28.1, 26.3, 25.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_4O_5Na$, 385.1488 found 385.1489.

(2*S*,3*R*)-2-(*N*-benzyoxycarbonyl)-amino-5-azido-3-*O*-formylo-pentanoic acid (8): An ice-cold solution of **7** (1 g, 2.76 mmol) in TFA-H_2O (20 mL, 9:1) was stirred for 15 min and at 25 °C for 7 h. Trifluoroacetic acid was co-evaporated with toluene at rotary evaporator using high vacuum to furnish hemiacetal as a thick liquid (crude wt = 0.9 g). To an ice-cooled solution of hemiacetal (0.9 g, 2.79 mmol) in acetone/water (10 mL, 5:1) was added sodium metaperiodate (0.89 g, 4.19 mmol), and the solution was stirred for 30 min at 25 °C. Ethylene glycol (0.2 mL) was added, solvent was evaporated on rotary evaporator and the residue was extracted with chloroform (3 × 15 mL). Usual workup afforded α-aminal as a thick liquid (1.5 g). To a stirred solution of above product (0.64 g, 2 mmol) in acetonitrile (5 mL) was added the solution of sodium dihydrogen phosphate (0.08 g, 0.59 mmol) in water (3 mL) and 30% H_2O_2 (0.24 mL, 2.4 mmol). Reaction mixture was stirred and cooled at –10 °C. To this solution, $NaClO_2$ (0.20 g, 2.4 mmol) in water (3.5 mL) was added drop wise over a period of 30 min and stirred at 15 °C, (the reaction was monitored by the evolution of oxygen with a bubbler connected to the apparatus). After 10 h, the reaction was decomposed by addition of a small amount of Na_2SO_3 (0.1 g) and acidified with 10% aq. HCl (5 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (4 × 5 mL). Combined organic layer was evaporated, and the residue was dissolved in 10% $NaHCO_3$ solution (25 mL). The bicarbonate layer was washed with ethyl acetate (15 mL) and then made acidic to pH 2 and extracted with ethyl acetate (3 × 15 mL). Usual workup gave **8** (0.64 g, 79% over 3 steps) as a sticky gum; R_f = 0.45 (40% EtOAc/pet. ether); $[\alpha]_D^{28}$ +24.4 (*c* 0.1, $CHCl_3$); IR (neat) ν max: 3389-2800 (br), 2150, 1721, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (1H, s, -*O*CHO), 7.41-7.20 (5H, m, Ar-H), 6.09-6.06 and 5.80-5.71 (1H, d, *J* = 8.9 Hz, 9.9 Hz, two rotamers) 5.20-5.05 (2H, m), 4.64-4.61 and 4.41-4.25 (3H, m, two rotamers), 3.49–3.12 (2H, m), 1.80–1.45 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 160.2, 157.1 and 156.7 (two rotamers) 135.8, 128.5, 128.6, 128.3, 128.1, 128, 71.1, 69.1, 67.7 and 67.5 (two rotamers), 58.2, 47.9 and 47.2 (two rotamers), 32.3, 30.5; (The ^{1}H and ^{13}C NMR spectra of **8** showed doubling of signals due to the presence of -*N*HCbz group resulting into restricted rotation around C=N bond); HRMS (ESI TOF) m/z calcd. for $C_{14}H_{16}N_4O_6Na$ $[M + Na]^+$ 359.0968, found 359.0964.

(2*S*,3*R*)-2,5-diamino-3-hydroxy-pentanoic acid.HCl (1): A steel pressure vessel containing **8** (0.2 g, 0.68 mmol) in MeOH (4 mL) and absolute HCl (1 mL) was purged with argon for 15 min and Pd/C (0.02g, 0.13 mmol) was added to this solution. The tube was pressurized to 100 psi with hydrogen gas. The reaction was stirred at room temperature for 4 days. The catalyst was removed by filtration through celite. The celite pad was washed several times with a MeOH:H_2O (2:1) solution. The water volume was reduced on high vacuum and brought to pH 6.5 with NH_4OH. Addition of EtOH resulted in a white precipitate that was collected by filtration and dried to yield 0.06 g (68%) of **1** as the mono-HCl salt; R_f = 0.4 (*n*-butanol /H_2O/AcOH = 4/2/1); mp 194-195 °C (dec.), (lit.[12d] mp 123 °C; $[\alpha]_D^{28}$ +3.2 (*c* 2.9, H_2O) [lit.[12d] $[\alpha]_D^{25}$+2.9 (*c* 3.0, H_2O)]; IR (neat) ν max: 3350 (br), 2950, 1640, 1572, 1540 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.20 (1H, ddd, *J* = 8.4, 5.3, 3.5 Hz), 3.73 (1H, d, *J* = 4.2 Hz), 3.30-3.07 (2H, sym m), 2.09 –1.71 (2H, m); ^{13}C NMR (75 MHz, D_2O) δ 172.8, 68.2, 59.8, 32.9, 31.8.; HRMS (ESI TOF) m/z calcd. for $C_5H_{12}N_2O_3Na$ $[M + Na]^+$ 171.0746, found 171.0750.

3,7-(*N*-benzyoxycarbonyl)-amino-1,2-*O*-isopropylidene-3,5,6,7-tetradeoxy-α-D-*xylo*-hept-5-ene-furanose (9): To a solution of **4** (0.3 g, 0.94 mmol) in dry dichloromethane (25 mL) was added *N*Cbz protected allylamine (0.54 g, 2.82 mmol) followed by 10 mol % Grubbs II[nd] generation catalyst (0.01 g, 0.01 mmol), the resulting reaction mixture was stirred for 72 h and solvent evaporation to get crude product (dark oil). Purification by column chromatography (pet. ether/ EtOAc = 6/4) gave **9** as a thick liquid (0.32 g, 70%); R_f = 0.4 (50% EtOAc/pet. ether); $[\alpha]_D^{28}$ –30.2 (*c* 1.9, $CHCl_3$); IR ν max: 3350 (br), 1733, 1650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.28 (10H, m), 5.97-5.86 (1H, m), 5.82 (1H, d, *J* = 3.7 Hz), 5.63-5.49 (1H, m), 5.19-4.92 (6H, m), 4.79 (1H, br. s), 4.61 (1H, br. s), 4.14 (1H, dd, *J* = 7.2, 2.3 Hz), 3.86-3.65 (2H, m), 1.53 (3H, s), 1.30 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 155.9, 136.5, 136.1, 131.0, 128.6, 128.5, 128.3, 128.1, 127.0, 124.8, 111.9, 103.9, 84.4, 77.6, 67.1, 66.8, 58.5, 42.5, 26.5, 26.1.; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{30}N_2O_7Na$, 505.1951; found 505.1946.

(2*S*,3*R*)-2,6-(*N*-benzyoxycarbonyl)-amino-3-*O*-formylo-hex-4-ene-oic acid (10): 9 afforded **10** as sticky gum (0.16 g, 68% over 3 steps) using similar procedure as described for the synthesis of **8** from **7**. R_f = 0.2 (40% EtOAc/pet. ether); $[\alpha]_D^{28}$ -48.3 (*c* 1.8, $CHCl_3$). IR ν max: 3350 (br), 2850, 1737, 1648, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (1H, s, -*O*CHO), 7.41-7.28 (10 H, m), 5.98 (1H, br. d, *J* = 5.4 Hz, -N*H*) 5.8-5.01 (3H, m), 5.60 (1H, d, *J* = 9.6 Hz), 5.30-5.10 (6H, m, two rotamers), 4.70 (1H,

dd, *J* = 6.2, 3.2 Hz), 4.31 (1H, d, *J* = 6.2 Hz), 3.81-3.60 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.9 (two rotamers), 162.8, 157.1, 157.0, 136.2, 133.4, 130.1, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 127.7, 127.0, 68.5, 68.2 (two rotamers), 67.1, 65.4, 42.3, 41.7.; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{24}N_2O_8Na$, 479.1430; found 479.1431.

(2*S*,3*R*)-2,6-Diamino-3-hydroxy-hexanoic acid. 2HCl (2): Compound **10** (0.16 g, 0.35 mmol) and 10% Pd/C (20% mole, 0.01 g, 0.07 mmol) in MeOH/HCl (4:1 mL) was stirred under a H_2 atmosphere at 100 psi for 12 h at 25 °C in pressure vessel. The catalyst was filtered through a pad of celite. The filtrate was concentrated, washed using EtOAc and purified using column chromatography using (H_2O/MeOH = 9.5/0.5) to afford **2** as a white powder (0.9 g, 81%); R_f = 0.06 (*n*-butanol /H_2O/AcOH = 4/1/1); mp 190–191 °C (The compound gets decomposed at metling point temperature) [reported[6a] mp 188–192 °C]; $[\alpha]_D^{28}$ +15.8, (*c* 1.88, CH_3OH); reported[6a] +16.9 (*c* 1.83, CH_3OH); IR (neat) ν max: 3355 (br), 1735 cm^{-1}; ^{1}H NMR (300 MHz, D_2O): δ 4.34-4.14 (1H, m), 4.06 (1H, s), 3.07 (2H, t, *J* = 6.9 Hz), 1.59–1.95 (4H, m); ^{13}C NMR (75 MHz, D_2O): δ 170.5. 68.4, 57.7, 38.9, 29.9, 23.3.; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_6H_{14}N_2O_3Na$, 185.0902; found 185.0910.

((2*R*,3*R*)-1,3-dihydroxypent-4-en-2-yl)-carbamate (11): An ice-cold solution of **4** (2 g, 5.74 mmol) in TFA-H_2O (20 mL, 9:1) was stirred for 15 min and at 25 °C for 4 h. Trifluoroacetic acid was co-evaporated with toluene at rotary evaporator using high vacuum to furnish hemiacetal as a thick liquid 1.8 g. To an ice-cooled solution of hemiacetal (1.8 g, 6.44 mmol) in acetone/water (20 mL, 5:1) was added sodium metaperiodate (2.07 g, 9.67 mmol), and the solution was stirred for 1.5 h at 25 °C. The solvent was evaporated on rotary evaporator, and the residue was extracted with EtOAc (3 × 15 mL). To an ice-cooled solution of crude aldehyde (1.5 g, 5.41 mmol) in THF-water (10 mL, 4:1) was added sodium borohydride (0.31 g, 8.11 mmol) in two portions. Reaction mixture was stirred for 30 min and quenched by adding saturated aq. NH_4Cl solution (5 mL). THF was evaporated under reduced pressure, extracted with chloroform (20 mL × 3) and concentrated. Purification by column chromatography (pet. ether/EtOAc = 7/3) gave **11** (1.2 g, 90%) as a thick colourless liquid; R_f = 0.45 (40% EtOAc/pet. ether); $[\alpha]_D^{25}$ –2.12, (*c* 1.8, $CHCl_3$); IR (neat) ν max: 3389 (br), 1636, 1460, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.24 (5H, m), 5.92-5.75 (1H, m), 5.62 (1H, d, *J* = 8.2 Hz), 5.38 (1H, d, *J* = 17.2 Hz), 5.26 (1H, br. d, *J* = 10.5 Hz), 5.11 (2H, br. s, C*H*$_2$O-), 4.41 (1H, br, s, -*N*H), 3.87-3.67 (3H, m), 3.45 (2H, br. s, exchange with D_2O); ^{13}C (125 MHz, $CDCl_3$) NMR: δ 157.0, 137.4, 136.3, 128.5, 128.2, 128.0, 116.5, 72.8, 72.5, 67.1, 63.5, 55.6; HRMS (ESI TOF) m/z calcd. for $[C_{13}H_{17}NO_4Na$ M + Na$]^+$ 274.1055, found 274.1057.

(2*R*,3*R*)-2-(((benzyloxy)carbonyl)-amino)-3-hydroxypent-4-en-1-yl-4-methylbenzenesulfonate (12): To a stirred solution of **11** (0.5 g, 1.99 mmol) in dry dichloromethane, was added triethyl amine (0.08 mL, 5.97 mmol) and tosyl chloride (0.42 g, 2.19 mmol) and catalytic amount of di-*n*butyl tinoxide (*n*Bu_2SnO) (0.01 g, 0.039 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Reaction mixture was quenched with water (5 mL). Organic layer was separated and aqueous layer was extracted with dichloromethane (10 mL × 3) and concentrated. Purification by column chromatography (pet. ether/ EtOAc = 8/2) gave **12** (0.69 g, 85%) as a thick liquid; R_f = 0.6 (40% EtOAc/pet. ether); $[\alpha]_D^{25}$ –2.41 (*c* 1.9, $CHCl_3$); IR (neat) ν max: 3341 (br), 1658, 1427, 1350, 1092, 756, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* = 8.1 Hz), 7.90-7.20 (7H, m), 5.86 -5.76 (1H, m), 5.32 (1H, d, *J* = 17.2 Hz), 5.28 (1H, d, *J* = 12.5 Hz), 5.20 (1H, br, s, exchange with D_2O), 5.11 (2H, s), 4.40 (1H, s, -*N*H), 4.10 (1H, dd, *J* = 9.7 Hz, 7.0 Hz), 4.09 (1H, dd, *J* = 9.8 Hz, 5.4 Hz), 4.01-3.80 (1H, m), 2.45 (3H, s); ^{13}C (125 MHz, $CDCl_3$) NMR: δ 156.4, 145.2, 136.5, 136.1, 132.4, 130.0, 128.6, 128.2, 128.0, 127.9, 117.2, 70.1, 68.1, 67.1, 53.5, 21.7.; HRMS (ESI TOF) m/z calcd. for $C_{20}H_{23}NO_6SNa$ $[M + Na]^+$ 428.1144, found 428.1139.

(2*R*,3*R*)-2-(((benzyloxy)-carbonyl)-amino)-3-(methoxymethyl)-pent-4-en-1-yl-4-methylbenzenesulfonate (13): DIPEA (0.44 mL, 2.52 mmol) was added at 0 °C to a cooled solution of the alcohol **12** (0.51 g, 1.26 mmol) in dry dichloromethane (15 mL) followed by MOM chloride (0.14 mL, 1.89 mmol). The reaction mixture was refluxed for 4 h. After completion of the reaction, solvent was evaporated and the residue was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (pet. ether/ EtOAc = 6/4) to give **13** (0.47 g 82%) as thick liquid; R_f = 0.6 (40% EtOAc/pet. ether); $[\alpha]_D^{25}$ –1.5 (*c* 1.64, $CHCl_3$); IR (neat) ν max: 1717, 1596, 1455, 1402, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80-7.61 (2H, d, *J* = 8.1 Hz), 7.39-7.29 (7H, m), 5.75-5.65 (1H, m), 5.33-5.27 (2H, m), 5.11 (1H, br, s, -*N*H), 5.09 (2H, s, -*O*CH_2OMe), 4.65 (1H, d, *J* = 6.7 Hz, -*O*CH_2Ph), 4.5 (1H, d, *J* = 6.7 Hz, -*O*CH_2Ph), 4.26- 4.22 (1H, m, -CH_2*O*Ts), 4.15 (1H, dd, *J* = 9.4 Hz, *J* = 7 Hz), 4.10 (1H, dd, *J* = 9.5 Hz, *J* = 5 Hz), 4.05-3.90 (1H, m), 3.33 (3H, s, -*O*CH_3), 2.46 (3H, s, -PhCH_3); ^{13}C (125 MHz, $CDCl_3$) NMR: δ 155.9. 145.0, 136.2, 133.6, 132.7, 129.1, 128.5, 128.2, 128.0, 127.9, 120.3, 94.1, 74.8, 67.8, 67.0, 55.9, 53.1, 21.6.; HRMS (ESI TOF) m/z calcd. for $C_{22}H_{27}NO_7SNa$ $[M + Na]^+$ 472.1406, found 472.1412.

((2*R*,3*R*)-1-(*N*-allylacetamido)-3-(methoxymethyl)-pent-4-en-2-yl)-carbamate (14): The tosylated compound **13** (0.35 g, 0.78 mmol), was stirred in a sealed tube with allylamine (5 mL) in methanol (5 mL) at 65 °C for 6 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (5 mL). Pyridine (1.0 mL) was added at 0 °C, followed by acetic anhydride (0.15 g, 0.99 mmol). The reaction mixture was stirred for 12 h. After completion of the reaction, it was diluted with ethyl acetate and organic layer was washed with sat. solution of $CuSO_4$. Organic layer concentrated in vaccum. The residue was chromatographed over silica gel (pet. ether/EtOAc = 7/3) to give divinyl product **14** (0.54 g, 93%) as colourless thick liquid; R_f = 0.7 (40% EtOAc/pet. ether); $[\alpha]_D^{25}$–0.44 (*c* 0.56, $CHCl_3$); IR (neat) ν max: 2105, 1713, 1628, 1475, 1417, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.30 (6H, m), 5.80-5.60 (2H, m), 5.50-5.01 (6H, m, two rotamers), 4.70 (1H, d, *J* = 6.7 Hz, -*O*CH_2Ph), 4.59 (1H, d, *J* = 6.7 Hz, -*O*CH_2Ph), 4.17-3.80 (5H, m, two rotamers), 3.41 (3H, s, -*O*CH_3), 3.16 (1H, d, *J* = 10 Hz), 1.99 (3H, s, -*N*$COCH_3$); ^{13}C (125 MHz, $CDCl_3$) NMR: δ 172.2, 156.6,

136.8, 134.1, 132.6, 128.6, 128.4, 128.0, 119.4, 116.7, 94.3, 66.5, 55.9, 53.5, 51.0, 45.9, 21.2. (The spectrum showed additional peaks due to its rotamers); HRMS (ESI TOF) m/z calcd. for $C_{20}H_{28}N_2O_5Na$ $[M + Na]^+$ 399.1896, found 399.1896.

((3*R*,4*R*)-1-acetyl-4-(methoxymethyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-yl)-carbamate (15): Grubbs catalyst II[nd] generation 10 mol % (0.03 g, 0.04 mmol) was added in two portions (after 1 h each) to a solution of **14** compound (0.15 g, 0.40 mmol) in dry CH_2Cl_2 (20 mL) and the reaction mixture was refluxed for 16 h. After completion of the reaction, solvent was removed and the residue was chromatographed over silica gel to furnish the tetrahydroazepine core (0.11 g, 78%); R_f = 0.3 (40% EtOAc/pet. ether). $[\alpha]_D^{25}$ −1.6 (*c* 1.9, $CHCl_3$); IR (neat) ν max: 2924, 1710, 1630, 1447, 1237cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.29 (8H, m), 6.24 (1H, d, *J* = 7.4 Hz), 6.10-6.03 (1H, m), 5.80-5.71 (2H, m), 5.62-5.01 (1H, m), 5.17 (1H, d, *J* = 12.2 Hz, -*O*CH_2OMe), 5.14-5.09 (1H, m), 5.06-5.03 (1H, d, *J* = 12.3 Hz, -*O*CH_2OMe), 4.71 (1H, d, *J* = 10.3 Hz, -*O*CH_2Ph), 4.65-4.60 (1H, m), 4.50 (1H, d, *J* = 10.3 Hz, -*O*CH_2Ph), 4.35-4.05 (3H, m, two rotamers), 3.93-3.80 (3H, m, two rotamers), 3.38 (3H, s, -*O*CH_3), 2.15 (3H, s, -*N*$COCH_3$); ^{13}C (125 MHz, $CDCl_3$) NMR: δ 171.5 and 170.5 (two rotamers), 156.2 and 155.6 (two rotamers), 136.8, 136.1, 132.8, 130.2, 128.6, 128.4, 128.2, 127.9, 126.2, 95.7, 75.6, 67.1, 67.05, 55.8, 55.5, 55.0, 52.8, 50.9, 49.2 21.3 and 21.1 (two rotamers) (The spectrum showed additional peaks due to its rotamers[14h]); HRMS (ESI TOF) m/z calcd. for $C_{18}H_{24}N_2O_5Na$ $[M + Na]^+$ 371.1583, found 371.1582.

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