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D-Glucose Based Synthesis of Proline-Serine C-C Linked Central and Right Hand Core of Kaitocephalin-a Glutamate Receptor Antagonist

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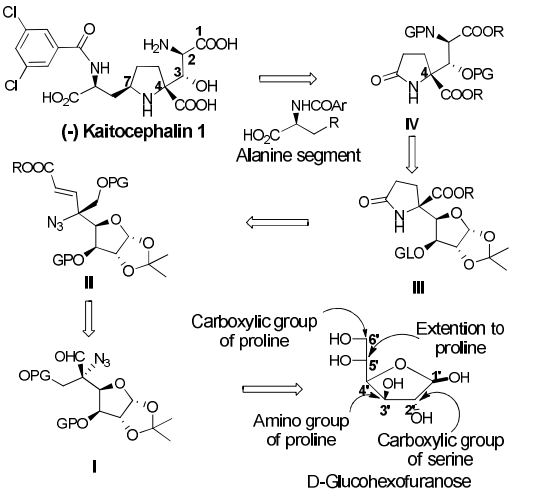
Synthesis of proline-serine core of kaitocephalin **1** has been accomplished starting from D-glucose. The C2 of D-glucose provided the carboxylic acid functionality of serine while; the amino- and β-hydroxy- groups of the serine fragment were amenable from C3 and C4 hydroxy groups of the sugar respectively. The key intermidiate to construct substituted proline with appropriate quaternary carbon framework of the target molecule was constructed by the Jocic-Reeve and Corey-Link reaction sequence with desired stereochemistry from C5-centre of D-glucose.

Introduction

Kaitocephalin **1** was isolated from the fungus *Eupenicillium shearii* in 1997 by Shin-ya et al.[1] It exhibits strong antagonist activity against AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazole-4-ylpropionate), KA (Kainic acid) and NMDA (N-methyl-D-aspartate) glutamate receptors that play a key role in many physiological processes such as neural plasticity, memory and learning[2]-thus rendering potential chemotherapeutic applications in epilepsy, stroke, Alzheimer's and Parkinson's diseases.[3] A molecular architecture of **1** is truncated in to three amino acid segments wherein; proline is the central part to which N-acyl alanine (left hand segment), and the serine (right hand fragment) are connected to the α'- and α-position of proline, respectively, through C-C bond (Scheme 1). The scare availability of **1** in nature, its importance in neurobiological studies and intriguing structural features has attracted ample attention for its synthesis. Till today, seven groups have independently reported the total synthesis of **1** or its analogues/fragments.[4] The challenging aspect in the synthesis of **1** is construction of the central trisubstituted proline core bearing quaternary stereogenic center at C4 connected to the hydroxymethyl carbon of the serine with requisite stereochemistry. In this direction, commonly used approach for the introduction of central and right hand segment of **1** is the alkylation of the substituted proline/pyroglutamate with the Garners aldehyde or equivalent to get C4 quaternary stereocenter with the C3-hydroxy group (Scheme 1). In other three asymmetric methods, central proline ring with requisite functionalities is constructed using (a) palladium catalyzed cyclization of oxiranylacrylate, (b) stereoselective desymmetrization of protected serinol and (c) rhodium catalyzed C-H amination protocols. As a part of our continuing efforts in the synthesis of natural products and its analogues using carbohydrate chemistry,[5] herein we report hitherto unknown chiral pool approach for the synthesis of trisubstituted proline segment (central) connected through C-C bond to the right hand serine fragment of kaitocephalin **1** starting from D-glucose.

Results and discussion

Recently, we reported synthesis of α-geminal dihydroxymethyl substituted piperidine and pyrrolidine iminosugars from the key intermediate **I** (Scheme 1), obtained from D-glucose, utilizing the Jocic-Reeve and Corey-Link reaction sequence.[6] Examination of intermediate **I** revealed the presence of C-C bonded proline and serine core (**IV**) of **1** with requisite absolute configuration at C-5'quaternary center (Scheme 1).



Scheme 1: Retrosynthesis of 1

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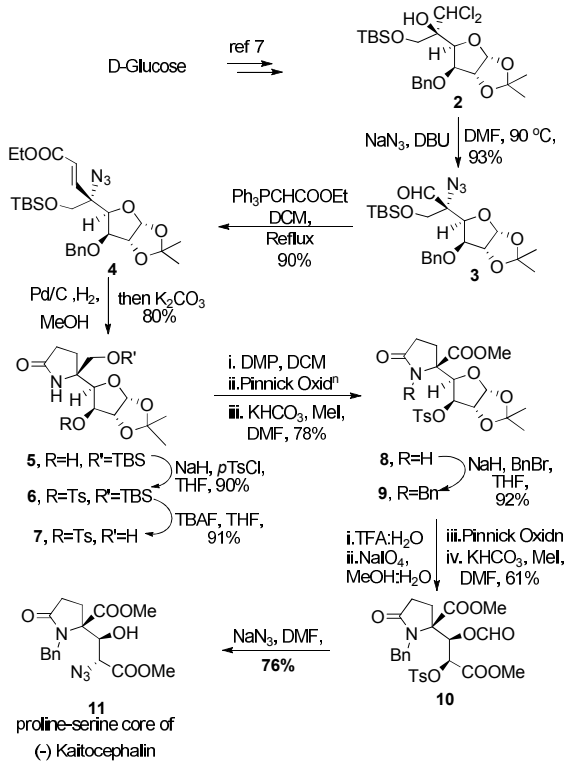
Electronic supplementary information (ESI) available: Figures giving ^{1}H and ^{13}C NMR spectra for all compounds and a CIF file giving crystallographic data for compound 8. CCDC 1415037 for ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

Thus, the proline core of **1** could be obtained from the C-5' azido aldehyde **I** by the Wittig olefination to get **II** followed by the lactamization and oxidation of the primary alcohol to get trisubstituted proline core (**III**). While, the rest of the D-glucose pendant could be judiciously manipulated to the serine fragment wherein; (a) the carboxylic group of serine (C1 of **1**) could be derived by excision of the reducing end (using oxidative cleavage of hemiacetal) followed by the oxidation and (b) the amino functionality of serine could be achieved by S_N2 displacement of C3'-*O*Ts by azido functionality of D-glucohexofuranose. The C4'-hydroxy of glucose is suitably placed with required absolute configuration of target molecule justifying the selection of D-glucohexofuranose as a starting material.

As shown in Scheme 2, the synthesis commenced with the dichloro D-glucohexofuranose **2** which is obtained from D-glucose in 38% overall yield.[7] Conversion of **2** to the C5' azido aldehyde **3** using NaN_3 in the presence of 1, 3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) and 15-crown-5 ether is known to give low yield.[7] In order to improve the yield, we have modified the reaction conditions. Thus, compound **2** on treatment with NaN_3 in DMF using 1.0 equiv. of DBU afforded C5'-azidoaldehyde **3** in 93% yield.



Scheme 2: Synthesis of **11**

In the next step, the Wittig olefination of **3** with ethyl 2-(triphenylphosphoranylidene)acetate afforded α,β-unsaturated ester **4** in good yield as exclusively *E*-isomer. Hydrogenation of **4** with 10% Pd-C in methanol under H_2 balloon atmosphere followed by addition of K_2CO_3 (0.3 equiv.) in the same pot (after complete disappearance of **4** on the TLC) and stirring for one hour at room temperature afforded lactam **5** in overall 80% yield in four step one pot reaction.[8] Subsequently, compound **5** was treated with NaH and *p*-toluenesulfonylchloride in dry THF at 0-30 °C for 2h that afforded C3'-*O*-tosylate **6** in 90 % yield.[9] In the next step, the C6'-silyl deprotection with anhydrous TBAF in THF gave primary alcohol **7** that on oxidation with the Dess-martin periodinane followed by the Pinnick oxidation ($NaClO_2$, NaH_2PO_4, 30% H_2O_2) and esterification ($KHCO_3$, MeI, DMF) gave methyl ester **8** in good yield. Fortunately, compound **8** was isolated as off white solid and X-ray crystallographic data (figure 1) indicated the absolute configuration at the quaternary carbon as 5' *R*. The lactam **8** was then protected as its *N*-benzyl derivative **9** by reacting with NaH and benzyl bromide in THF at 0-30 °C.[10] Finally, hydrolysis of 1, 2-*O*-isopropylidene group in **9** using TFA: H_2O (3:1) gave hemiacetal that was immediately subjected to the oxidative cleavage using $NaIO_4$ followed by the Pinick oxidation and esterification ($KHCO_3$, MeI, DMF) furnished *O*-formate 10.[11] The S_N2 dispalcement of *O*-tosylate in **10** using NaN_3 in DMF at 50 °C afforded *N*-benzyl protected proline and serine segment **11** of kaitocephalin **1**. The construction of left hand alanine fragment on *N*-debenzylated proline-serine segment **11**, leading to the formation of kaitocephalin **1** is known.[4b]

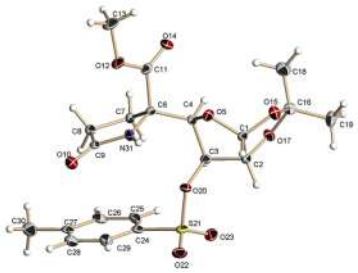


Figure 1: ORTEP diagram of compound **8**

Conclusions

In conclusion, we have developed a new chiral pool strategy for the synthesis of C-C linked proline-serine fragment of kaitocephalin from D-glucose. Our methodology is totally different from that of known methods and addresses the synthesis of challenging central tri-substituted proline core, with quaternary stereogenic center, using Jocic-Reeve and Corey-Link approach with 5-ketoglucohexose followed by building proline ring with requisite functionalities. Easy access for the manipulation of functional groups in D-glucohexofuranose, simple chemical transformations with complete diastereoselectivity make this strategy useful one for the total synthesis of kaitocephalin or its analogues and work in this direction is in progress.

Experimental

General Experimental Methods

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with a FTIR as a thin film or using KBr pellets and are expressed in cm^{-1}. ^1H (300, 500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded using $CDCl_3/D_2O$ as a solvent. Chemical shifts were reported in δ units (ppm) with reference to TMS as an internal standard and *J* values are given in Hz. High resolution mass spectra (HRMS) were obtained in positive ion electrospray (ESI) mode using TOF (time of flight) analyzer. Optical rotations were measured on a JASCO P-1020 digital polarimeter with sodium light (589.3 nm) at 25-30 °C. Thin layer chromatography was performed on pre-coated plates. Column chromatography was carried out with silica gel (100-200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol and THF were purified and dried before use. Distilled *n*-hexane and ethyl acetate were used for column chromatography. After quenching of the reaction with water, the work-up involves washing of combined organic layers with water, brine, drying over anhydrous sodium sulphate and evaporation of the solvent at reduced pressure.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-deoxy-5-azido-5-*C(S)*-(tert-butyldimethylsilyloxy)methyl-α-D-*gluco*-hexodialdo-furanose 3

To a stirred solution of **2** (2 g, 3.94 mmol) in dry DMF (15 mL) under N_2 blanket was added NaN_3 (1.28 g, 19.70 mmol) followed by addition of DBU (0.58 mL, 3.9 mmol). Resulting pale brown solution was then heated at 90 °C till consumption of starting material (2 hr, monitored by TLC). Reaction mixture was then poured in water and extracted with ethyl acetate (3 x 20 mL) organic layer was washed with water, brine and was then dried over anhydrous sodium sulphate. Evaporation of solvent and purification using column chromatography (n-hexane/ethyl acetate =9.5/0.5) gave **3** (1.75 g, 93.5 %) as viscous oil: R_f 0.55 (*n*-hexane/ethyl acetate = 9/1); $[\alpha]_D^{28.5}$ = -24 (*c* 1.03, $CHCl_3$); IR (neat) 1732 cm^{-1}, 2123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H, CHO), 7.20-7.42 (m, 5H, Ar-H), 5.98 (d, *J*=3.6 Hz, 1H, H1), 4.60-4.7- (m, 2H, H4, CH2a-Ph), 4.47 (d, *J*=3.6 Hz, 1H, H2), 4.45 (d, *J*=11.5 Hz, 1H, CH2b-Ph), 4.00-4.10 (m, 2H, H3, CH2aOTBS), 3.88 (d, *J*=10.5 Hz, 1H, CH2bOTBS), 1.46 (s, 3H, CH3), 1.33 (s, 3H, CH3), 0.84 (s, 9H, 3CH3), 0.03 (s, 3H, CH3), -0.01 (s, 3H, CH3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 136.2, 128.6, 128.3, 128.2, 112.4, 105.0, 82.0, 81.9, 80.9, 72.2, 71.5, 64.0, 26.9, 26.5, 25.6 (strong, 3C), 25.6, 18.0, -5.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{35}N_3NaO_6Si$ 500.2187; Found 500.2187.

Ethyl-(1,2-*O*-Isopropylidene-3-*O*-benzyl-5-deoxy-5-azido-5-*C(S)*-(tert-butyldimethylsilyloxy) methyl -6,7-dideoxy-6(*E*)-ene-α-D-*gluco*-octofurano)-uronate 4

Compound **3** (1.5 g, 3.14 mmol) was dissolved in DCM (20 mL) to which ethyl 2-(triphenylphosphoranylidene)acetate (1.36 g, 3.92 mmol) was added and refluxed reaction mixture for 5 hr. After completion of reaction solvent was evaporated and purification by column chromatography gave (n-hexane/ethyl acetate =9/1) gave **4** (1.53 g, 89.5 %) as viscous oil: R_f 0.4 (*n*-hexane/ethyl acetate = 9/1); $[\alpha]_D^{28.0}$ = 1 (*c* 0.5, $CHCl_3$); IR (neat) 1658 cm^{-1}, 1718 cm^{-1}, 2113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 5H, Ar), 7.01 (d, *J* = 15.8 Hz, 1H, H8), 6.08 (d, *J* = 15.8 Hz, 1H, H7), 5.92 (d, *J* = 3.7 Hz, 1H, H1), 4.64 (d, *J* = 11.7 Hz, 1H, CHa-Ph), 4.56 (d, *J* = 3.7 Hz, 1H, H2), 4.45 (d, *J* = 3.1 Hz, 1H, H3), 4.41 (d, *J* = 11.7 Hz, 1H, CHb-Ph), 4.15 (q, *J* = 6.25 Hz 2H, O-CH2), 3.99 (d, *J* = 3.1 Hz, 1H, H4), 3.71 (ABq, *J* = 10.1 Hz, 2H, H5), 1.43 (s, 3H), 1.27 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 1H),. 0.82 (s, 9H), 0.00 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.00 (C=O), 143.84 (Ar), 136.81 (Ar), 128.55 (Ar), 128.06 (C7), 127.91 (Ar), 123.36 (C8), 111.97 (C13), 104.68 (C1), 82.26 (C2), 81.66 (C3), 80.35 (C4), 71.96 (CH2-Ph), 66.45 (C6), 60.48 (O-CH2CH3), 26.83 (C5), 26.40 (C11), 25.69 (tBu), 18.06 (CH3), 14.22 (CH3), -5.63 (Si-CH3), -5.72 (Si-C). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{41}N_3NaO_7Si$ 570.2606; Found 570.2600.

1,2-*O*-isopropylidene-3-hydroxy-5-deoxy-5-*C(S)*-(3-pyrolidinone)-6-(tertbutyldimethylsilyloxy)methyl-α-D-*gluco*-hexofuranose 5

To a stirred solution of **4** (1.5 g, 2.741 mmol) in methanol was added 10% Pd/C and stirred reaction mixture under H_2 (balloon pressure) at rt. After 12 hr K_2CO_3 (0.15 g) was added to reaction mixture and stirred reaction for additional 1 hr. Reaction mixture was then filtered off over celite, filtrate was evaporated to give crude product which was purified using column chromatography (n-hexane/ethyl acetate =1/1 then 1/9) to give lactone **5** (0.85 g, 80.18 %) as white solid: mp 203-205 °C, R_f 0.15 (*n*-hexane/ethyl acetate = 1/1) $[\alpha]_D^{28.7}$ = -20.17 (*c* 0.23, $CHCl_3$); IR (neat) 1680.77 cm^{-1}, 2930.04 cm^{-1}, 3317.80 cm^{-1} (broad). ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (brs, 1H, NH), 5.96 (d, *J* = 3.7 Hz, 1H, H1), 4.52 (d, *J* = 3.7 Hz, 1H, H2), 4.52-4.40 (bs, 1H, OH, exchanges with D_2O). 4.26 – 4.24 (m, 1H, H3, after D2O exchange appeared as d with J= 2.70 Hz), 4.14 (d, *J* = 2.7 Hz, 1H, H4), 3.70 (d, *J* = 9.9 Hz, 1H, H6a), 3.63 (d, *J* = 9.9 Hz, 1H, H6b), 2.52 – 2.34 (m, 2H, H8), 2.29 – 2.16 (m, 1H, H7a), 2.12 – 2.02 (m, 1H, H7b), 1.49 (s, 3H, CH3), 1.32 (s, 3H, CH3), 0.91 (s, 9H, tBu), 0.11 (s, 6H, 2 X SiCH3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.81 (CONH), 111.54 (C10), 104.59 (C1), 85.44 (C4), 81.97 (C2), 75.31 (C3), 67.32 (C6), 63.28 (C5), 30.04 (C8), 26.80 (CH3), 26.17 (C7), 25.79 (tBu), 18.19 (CH3), -5.53(Si-CH3), -5.64 (Si-C). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{33}NNaO_6Si$ 410.1969; Found 410.1958.

1,2-*O*-Isopropylidene-3-*O*-tosyl-5-deoxy-5-*C(S)*-(2-(5-oxo-pyrolidine))-6-(tertbutyldimethylsilyloxy)methyl-α-D-*gluco*-hexofuranose 6

Solution of **5** (0.8 g, 2.06 mmol) in dry THF (10 mL) was added drop wise to a pre-cooled solution of NaH (1.08 g, 4.53 mmol) in dry THF (5 mL) under N_2 blanket and stirring was continued for 20 min after complete addition. Then *p*-Tosyl chloride (0.430 g, 2.26 mmol) was added to reaction mixture and stirred reaction mixture for additional 1.5 hr. After complete consumption of starting material (monitored by TLC) saturated solution of NH_4Cl was added carefully and extracted with ethyl acetate (3 X 10 mL). Organic phase washed with brine, dried over anhydrous sodium sulphate, evaporation of solvent and purification by column chromatography (n-hexane/ethyl

acetate =7/3) gave **6** (1 g, 90.1 %) as thick liquid: R_f 0.6 (*n*-hexane/ethyl acetate = 1/1); $[\alpha]_D^{28.7}$ = 10.42 (*c* 0.47, $CHCl_3$); IR (neat) 1697.70 cm^{-1}, 2927.54 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 1H, Ar), 7.41 (d, *J* = 8.2 Hz, 1H, Ar), 5.91 (d, *J* = 3.8 Hz, 1H, H1), 5.77 (brs, 1H, NH), 4.99 (d, *J* = 2.7 Hz, 1H, H3), 4.59 (d, *J* = 3.8 Hz, 1H, H2), 4.39 (d, *J* = 2.7 Hz, 1H, H4), 3.51 (ABq, *J* = 10.1 Hz, 2H,H6), 2.49 (s, 3H, CH3-Ar), 2.33 – 2.24 (m, 2H, H8), 2.21-2.14 (m, 1H, H7a), 1.80 – 1.66 (m, 1H, H7b), 1.46 (s, 3H, CH3), 1.28 (s, 3H, CH3), 0.89 (s, 9H, tBu), 0.06 (s, 6H, 2 X Si-CH3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8 (CONH), 145.8 (Ar), 132.9 (Ar), 130.2 (Ar), 127.8 (Ar), 112.2 (C10), 104.0 (C1), 83.0 (C2), 81.7 (C3), 79.3 (C4), 67.5 (C6), 62.9 (C5), 29.9 (C8), 26.4 (CH3), 26.2 (CH3), 25.7 (t-Bu), 24.4 (C7), 21.7 (Ar-CH3), 17.9 (C-(CH3)), -5.6 (Si-CH3), -5.6 (Si-C). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{39}NNaO_8SSi$ 564.2058; Found 564.2057.

1,2-*O*-Isopropylidene-3-*O*-tosyl-5-deoxy-5-*C(S)*(2-(5-oxo-pyrolidine))-α-D-*gluco*-hexofuranose 7

To a stirred solution of compound **6** (0.9 g, 1.66 mmol) in THF (10 mL) was added 1M solution of TBAF in THF (2 mL, 1.9 mmol) at 0 °C. Stirred reaction mixture for 1hr, after completion of reaction quenched with saturated solution of NH_4Cl (5 mL) and extracted with ethylacetate (3 X 10 mL). Evaporation of solvent and column chromatography purification (n-hexane/ethyl acetate =1/1, 1/9) gave **7** (0.65 g, 91.5 %) as colorless solid: mp 120-123 °C R_f 0.45 (ethyl acetate) $[\alpha]_D^{27.8}$ = 4.68 (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1697.70 cm^{-1}, 2927.54 cm^{-1}. IR (neat) 1664.51 cm^{-1}, 3241.73 cm^{-1} (broad). ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H, Ar), 7.42 (d, *J* = 8.0 Hz, 1H, Ar), 6.62 (brs, 1H, exchanges with D2O), 5.92 (d, *J* = 3.8 Hz, 1H, H1), 5.03 (d, *J* = 2.8 Hz, 1H, H3), 4.62 (d, *J* = 3.8 Hz, 1H, H2), 4.37 (d, *J* = 2.8 Hz, 1H, H4), 3.62 (t, J= 8.0 Hz, 1H, exchanges with D_2O), 3.45-3.40 (m, 2H,H6, after D_2O exchanges appear as ABq, *J* = 11.6 Hz, 2H, H6), 2.48 (s, 3H, CH3), 2.35 – 2.22 (m, 2H, H8), 2.20 – 2.11 (m, 1H, H7), 1.78 – 1.68 (m, 1H, H7), 1.47 (s, 3H, CH3), 1.27 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 178.01 (CONH), 145.93 (Ar), 132.7(Ar), 130.27(Ar), 127.94(Ar), 112.50 (C10), 104.05 (C1), 83.11 (C2), 81.71 (C3), 79.71 (C4), 66.90 (C6), 63.81 (C5), 30.36 (C8), 26.48 (CH3), 26.20 (CH3), 24.65 (C7), 21.79 (Ar-CH3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{25}NNaO_8S$ 450.1193; Found 450.1191.

Methyl-(1,2-*O*-Isopropylidene-3-*O*-tosyl-5-deoxy-5-*C(S)*-(2(5-oxo-pyrolidine))-α-D-*gluco*-hexofurano)-uronate 8

Compound **7** (0.6 g, 1.40 mmol) was dissolved in DCM and cooled to 0 °C, to this cooled solution then DMP (0.893 g, 2.10 mmol) was added and stirred reaction mixture for 12 hr while allowing to come for rt. After completion of reaction, reaction mixture was washed with saturated solution of $NaHCO_3$. Organic phase was dried and evaporated to give 0.59 g of crude aldehyde as thick liquid. This aldehyde (0.59 g) was dissolved in acetonitrile (10 mL) to which added solution of NaH_2PO_4 (0.043 g, 0.276 mmol) and 30 % H_2O_2 (0.17mL, 1.51 mmol) in water (5 mL). The mixture was cooled to 0 °C, $NaClO_2$ (0.187g, 2.07 mmol) in water (5 mL) was added drop wise over period of 15 min and stirred at rt till completion of reaction (12 hr). Reaction mixture was treated with sodium sulfite and extracted with ethyl acetate (3 X10 mL). Evaporation of solvent gave acid (0.6 g) as thick foam. This acid obtained was dissolved in dry DMF (8 mL) to which added $KHCO_3$ (0.27 g, 2.7 mmol) and cooled to 0 °C. MeI (0.1 mL, 1.68 mmol) was added drop wise to mixture and stir for 2 hr while allowing to come for rt. After completion of reaction poured in water and extracted with ethyl acetate. Evaporation of solvent and column chromatography purification (n-hexane/ethyl acetate =7/3) gave compound **8** (0.5g, 78.12 %) as off white solid: mp = 170-173 °C; R_f 0.6 (*n*-hexane/ethyl acetate = 1/1) $[\alpha]_D^{28.0}$ = 12.22 (*c* 0.7, $CHCl_3$); IR (Neat) 1695.70 cm^{-1}, 1737.70 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H, Ar), 7.42 (d, *J* = 8.2 Hz, 2H, Ar), 5.93 (d, *J* = 3.7 Hz, 1H, H1), 5.91 (s, 1H, NH) 5.09 (d, *J* = 3.1 Hz, 1H, H3), 4.63 (d, *J* = 3.7 Hz, 1H, H2), 4.58 (d, *J* = 3.1 Hz, 1H, H4), 3.74 (s, 3H, CO_2CH3), 2.49 (s, 3H, CH3-Ar), 2.35 – 2.25 (m, 4H, H5,H6), 1.50 (s, 3H), 1.30 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 176.51 (COOMe), 171.88 (CONH), 145.95 (Ar), 132.36 (Ar), 130.16 (Ar), 128.16 (Ar), 112.82 (C10), 104.42 (C1), 83.06 (C3), 80.88 (C2), 80.18 (C4), 64.82 (C5), 53.23 (COOCH3), 29.18 (C8), 27.15 (C7), 26.71 (CH3), 26.31 (CH3), 21.79 (Ar-CH3).. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{25}NNaO_9S$ 478.1142; Found 478.1149.

Methyl-(1,2-*O*-Isopropylidene-3-*O*-tosyl-5-deoxy-5-*C(S)*-(2-(*1*-benzyl-5-oxo-pyrolidine))-α-D-*gluco*-hexofurano)-uronate 9

Solution of **8** (0.15 g, 0.32 mmol) in dry THF (3 mL) was added drop wise to a pre-cooled solution of NaH 60 % oil suspension (0.016 g, 0.41 mmol) in dry THF (3 mL) under N_2 blanket and stirring was continued for 20 min after complete addition. Then Benzyl bromide (0.041 mL, 0.35 mmol) was added to reaction mixture and stirred reaction mixture for additional 1.5 hr. After complete consumption of starting material (monitored by TLC) saturated solution of NH_4Cl (5 mL) was added carefully and extracted with ethyl acetate (3 X 5 mL). Organic phase washed with brine, dried over anhydrous sodium sulphate, evaporation of solvent and purification by column chromatography (n-hexane/ethyl acetate = 8/2) gave **9** (0.165 g, 91.66 %) as colorless solid: mp 80-85 °C R_f 0.4 (*n*-hexane/ethyl acetate = 7/3) $[\alpha]_D^{28.0}$ = 9.7(*c* 0.34, $CHCl_3$); IR (Neat) 1695.65 cm^{-1}, 1738.73 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H, Ar), 7.35 (d, *J* = 8.0 Hz, 2H, Ar), 7.35 – 7.10 (m, 5H), 5.94 (d, *J* = 3.8 Hz, 1H, H1), 5.21 (d, *J* = 3.2 Hz, 1H, H3), 4.85 (d, *J* = 15.7 Hz, 1H, CHaPh), 4.71 (d, *J* = 3.3 Hz, 1H, H4), 4.69 (d, *J* = 3.8 Hz, 1H, H2), 4.06 (d, *J* = 15.7 Hz, 1H, CHbPh), 3.10 (s, 3H, CO2CH3), 2.62 – 2.51 (m, 1H, H7a), 2.50 – 2.38 (m, 5H, CH3-Ar, H7b,H6a), 2.1 – 2.0 (m, 1H, H6b), 1.41 (s, 3H, CH3), 1.30 (s, 3H, CH3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.93 (COOMe), 170.61 (CONH), 145.53, 135.87, 132.72, 130.03, 128.31, 128.23, 127.98, 127.46, 112.42 (C10), 104.13 (C1), 83.50 (C3), 83.27 (C2), 76.00 (C4), 68.73 (C5), 52.07 (COOCH3), 43.99 (CH2-Ph), 29.67 (C8), 26.77 (CH3), 26.22 (CH3), 24.43 (C7), 21.71 (Ar-CH3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{31}NNaO_9S$ 568.1612; Found 568.1617.

(*R*)-methyl-1-benzyl-2-((1*R*,2*S*)-1-(formyloxy)-3-methoxy-3-oxo-2-(tosyloxy)propyl)-5-oxopyrrolidine-2-carboxylate 10

A solution of **9** (0.15 g, 0.27 mmol) in TFA–H2O (3.00 mL, 3:1) was stirred at 0 ^{o}C for 6 h. Azeotropic removal of TFA with toluene *in vacuo* afforded the intermediate hemiacetal (0.135 g, thick liquid), which was taken in MeOH/water (6 mL, 9:1), cooled to 0 ^{o}C and $NaIO_4$ (0.088g, 0.41 mmol) added. After stirring for 5 h, the reaction mixture was concentrated in vacuo, the residue extracted with CHCl3 (3 X 10 mL), and the extract concentrated *in vacuo* to get the crude aldehyde (0.1g, thick liquid). This was dissolved in MeCN (5 mL), treated successively with NaH_2PO_4 (0.006g, 0.039 mmol) in H_2O (1 mL) and 30% H_2O_2 (0.021 mL, 0.218 mmol), cooled to 0 ^{o}C, and $NaClO_2$ (0.026 g, 0.298 mmol) in H_2O (1.5 mL) added into it in 10 min. After stirring at 20 ^{o}C till completion of the reaction (10 h,), the reaction mixture was treated with sodium sulphite, and extracted with EtOAc (3 X 5 mL). Concentration of the extract *in vacuo* to get acid (0.089 g). The crude acid was dissolved in dry DMF (5 mL), added $NaHCO_3$ (0.027 g, 0.32 mmol) followed by MeI (0.012 mL, 0.20 mmol) at 0 ^{o}C. After completion of reaction, usual workup and purification by column chromatography (n-hexane/ethyl acetate =1/1) of the residue gave **10** (0.085g, 60.71 %) as thick liquid: R_f 0.5 (*n*-hexane/ethyl acetate = 1/1), $[\alpha]_D^{26.8}$= 52.38 (*c* 1.09 $CHCl_3$); IR (Neat) 1693.85 cm^{-1}, 1729.15 cm^{-1}, 1744.23 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H, OCHO), 7.78 (d, *J* = 7.7 Hz, 2H, Ar), 7.35 (d, *J* = 7.7 Hz, 2H, Ar), 7.30-7.20 (m, 5H, Ar), 6.13 (s, 1H, H1), 5.61 (s, 1H, H2), 4.92 (d, *J* = 15.7 Hz, 1H, CHaPh), 3.98 (d, *J* = 15.7 Hz, 1H, CHbPh), 3.64 (s, 3H, CO2CH3), 3.15 (s, 3H, CO2CH3), 2.70 – 2.49 (m, 4H, H4,H5), 2.46 (s, 3H, CH3Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.29 (CONH), 170.05(COOMe), 166.16 (COOMe), 158.48 (OCOH), 145.77,() 135.66, 132.43, 129.85, 128.50, 128.32, 128.29, 127.64, 75.24 (C1), 69.32 (C2), 68.40 (C3), 53.12 (COOCH3), 52.56 (COOCH3), 43.86 (CH2-Ph), 29.42 (C5), 23.42 (C4), 21.74 (Ar-CH3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NNaO_{10}S$ 556.1246; Found 556.1253.

(*R*)-Methyl-2-((1*S*,2*R*)-2-azido-1-hydroxy-3-methoxy-3-oxopropyl)-1-benzyl-5-oxopyrrolidine-2-carboxylate 11

To a stirred solution of tosylate **10** (0.05) in DMF was added NaN_3 and resulting turbid solution was stirred at 50 ^{o}C for 6 hr. After completion of reaction, poured reaction mixture in water and extracted with ethyl acetate. Drying, evaporation of organic extract *in vacuo* and purification by column chromatography (n-hexane/ethyl acetate =1/1) of the residue gave **11** (0.029g, 76.25 %) as thick liquid: R_f 0.56 (*n*-hexane/ethyl acetate = 1/1); $[\alpha]_D^{29.1}$ = 32.1 (*c* 0.39 $CHCl_3$); IR (Neat) 1693.85 cm^{-1}, 1744.23 cm^{-1}, 2120.21 cm^{-1}, 3400 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.26 (m, 5H, Ar), 4.62 (d, *J* = 15.24 Hz, 1H, Bn), 4.35 (d, *J* = 15.24 Hz, 1H, Bn), 4.00 (d, *J* = 2.22 Hz, 1H,H3), 3.75 (d, *J* = 2.2 Hz, 1H, H2), 3.55 (s, 3H, COOCH3), 3.48(s, 3H, COOCH3), 2.65 – 2.34 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.51 (CONH), 171.88(COOMe), 166.16 (COOMe), 145.95(Ar), 132.32(Ar), 129.85(Ar), 128.50(Ar), 128.43(Ar), 75.29 (C2), 68.24 (C3), 62.56(C1), 53.42 (COOCH3), 52.56 (COOCH3), 43.12 (CH2-Ph), 29.86 (C5), 23.42 (C4). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{20}N_4NaO_6$ 399.1281; Found 399.1278.

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8 In this reaction, we have isolated the un-cyclized product with reduction of the azide, olefin groups along with C3 *O*-debenzylation as evident from the ^{1}H NMR. Addition of 0.3 equiv. K_2CO_3 in the same pot provided required lactam.

9 Tosylation of compound **5** using *p*-tolunesulfonylchloride in dichloromethane, pyridine/ TEA with catalytic amount of DMAP under variety of reaction conditions was unsuccessful.
10 Hydrolysis of 1,2-*O*-isopropylidine group in **9** using TFA: H_2O gave hemiacetal, that on oxidative cleavage using $NaIO_4$ followed by the Pinnick oxidation gave complex mixture. Therefore, we protected lactam **9** as its benzyl derivative.
11 Formation of *O*-formate was confirmed by the NMR analysis which showed singlet at δ 7.86 in the ^{1}H NMR and δ 158.5 in the ^{13}C NMR corresponding to the formate group.