Towards the synthesis of pyloricidins: synthesis of (2*S*,3*R*,4*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2,3,4,6-tetrahydroxyhexanoyl-*β*-D-phenylalanine methyl ester

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Dedicated to Professor S. Swaminathan on his 80th birthday

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Abstract

Highly practical and efficient synthesis of (2*S*,3*R*,4*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2,3,4,6-tetrahydroxyhexanoyl-*β*-D-phenylalanine methyl ester was achieved using easily available Garner aldehyde and phenylglycine, which is an advanced intermediate for the synthesis of pyloricidins.

Keywords: Amino acids, antibiotic, dihydroxylation, homologation, debenzylation

Introduction

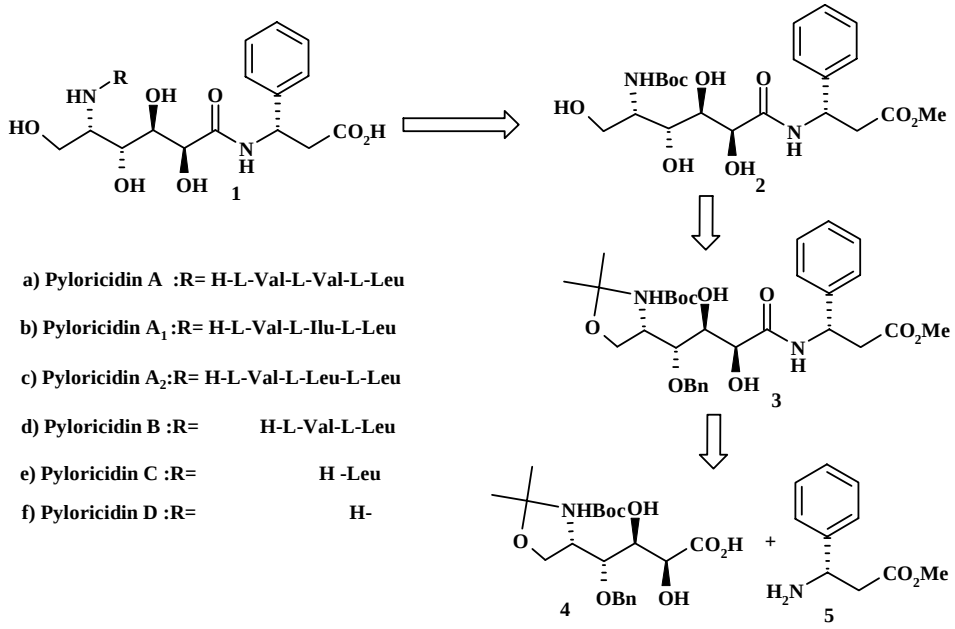
The pyloricidins **1**, isolated[1] from soil samples of *Bacillus sp*. HC-70 and *Bacillus sp.* HC-72, have shown exceptional anti-*Helicobacter pylori* antibiotic properties.[2] *Helicobacter pylori*, a gram-negative bacterium, infection of this is the major causative factor of a number of gastric and duodenal pathologies. Several classes of compounds have been identified as anti-*H. Pylori* agents. Incomplete eradication of *H. pylori* has been achieved with some anti-microbial agents such as amoxicillin and clarithromycin due to their degradation by gastric acid. Efforts have been directed to develop or isolate new series of compounds having antibiotic properties, which can totally eradicate this bacteria.[3] Naturally, the pyloricidin class of molecules have attracted attention of synthetic and medicinal chemistry groups. The first synthesis of pyloricidin **1** has recently been achieved by Hasuoka *et al*., using chiron approach starting from D-galactosamine hydrochloride.[4]

As a part of our continued interest in developing simple and elegant strategies for the synthesis of bioactive natural and unnatural products,[5] especially combining chiron approach with asymmetric synthesis, herein, we disclose the full findings on the N- and C- terminal

protected (2*S*,3*R*,4*R*,5*S*)-5-amino-2,3,4,6-tetrahydroxyhexanoyl phenylalanine, which constitutes the key backbone of pyloricidins. This synthesis was taken up as part of designing new hybrid analogues of peptide bioactives. The easily available L-phenylglycine **13** and Garner aldehyde **6** were effectively transformed to the target compound **2** involving very straightforward transformations.

Results and Discussion

In formulating the synthetic plan for **2**, we envisioned an amide bond formation between the acid **4** and amine **5**, followed by deprotection of acetonide and benzyl groups allowing the synthesis of target compound **2** (scheme 1).

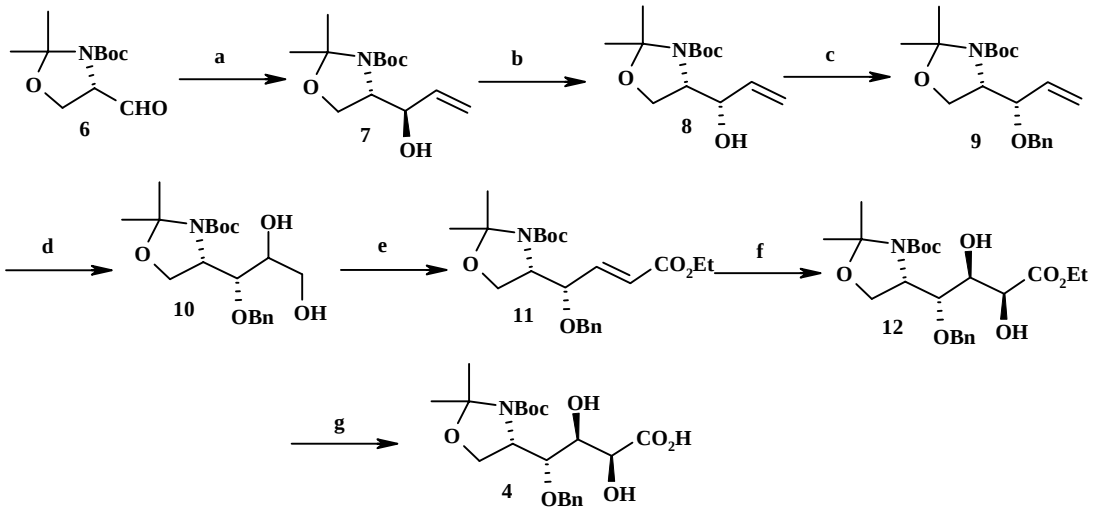


Scheme 1

Synthesis of acid **4** started from readily available Garner aldehyde **6**.[6] Grignard reaction of Garner aldehyde **6** with vinylmagnesium bromide in tetrahydrofuran at –78 °C gave the allyl alcohols **8** and **7** with 1:6 *syn-anti* selectivity.[7] The two diastereomers were separated by silica gel column chromatography. The ratio of the isomers was determined based on the weight of products isolated. Inversion of hydroxy group in alcohol **7** under Mitsunobu conditions[8] using triphenylphosphine/diethyl azodicarboxylate and 4-nitrobenzoic acid in THF at 0 ^{o}C to room temperature and followed by hydrolysis of nitro benzoate with K_2CO_3 in MeOH produced the *syn* alcohol **8** in 30% yield for two steps. The spectral data (optical rotation and ^{1}H NMR) of compound **8** and minor diastereomer obtaind during vinylation of Garner aldehyde were

comparable confirming the inversion of hydroxy group. Allylic hydroxy group of compound **8** was protected as benzyl ether using NaH and benzyl bromide in THF. Dihydroxylation of olefin **9** using OsO_4 and NMO in acetone: H_2O (8:2) afforded the diol **10**. After periodate oxidation of diol **10**, the resultant aldehyde was treated with (carboethoxymethylene)triphenylphosphorane in benzene to afford the unsaturated ester **11**. Ester **11** was dihydroxylated using OsO_4 and NMO in acetone:water (8:2) to furnish the diol **12** with 13:1 diastereomeric ratio.[9] This ratio was determined using hypersil OD reverse phase column and MeOH: water / 70: 30 as eluents at 254 nm.

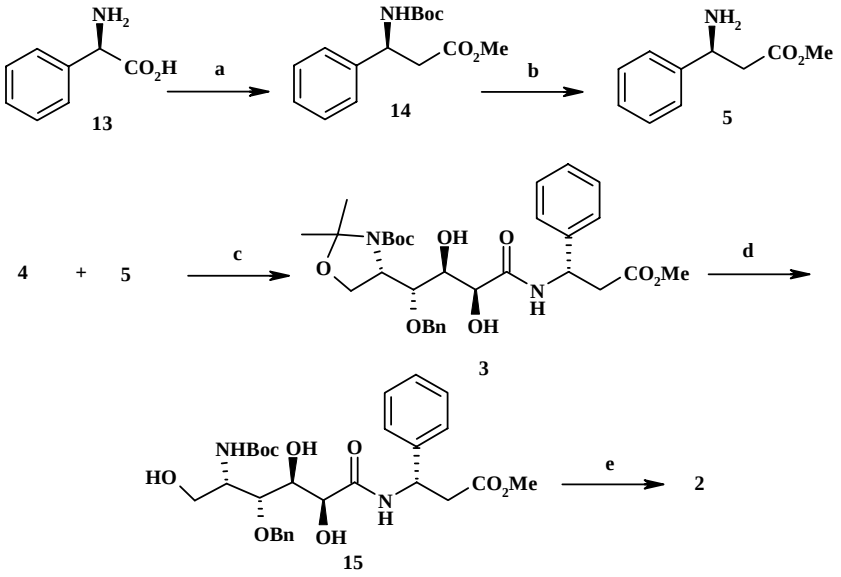
Hydrolysis of the diol **12** using $LiOH.H_2O$ gave the dihydroxy acid **4** (Scheme 2).



a) Vinylmagnesium bromide, THF, -30 °C; b) i. 4-nitrobenzoic acid, DEAD,TPP,THF; ii. K_2CO_3, MeOH; c) NaH, BnBr,THF; d) OsO_4, NMO, acetone:water (8:2); e) i. $NaIO_4$, THF:water(8:2); ii. C_2 - Wittig f) OsO_4, NMO, acetone:water(8:2); g) $LiOH.H_2O$, THF.

Scheme 2

β-Phenylalanine methyl ester **5** was prepared from phenylglycine **13**.[10] Homologation of *N*-Boc protected phenyl glycine with ethyl chloroformate, triethylamine, CH_2N_2 and silverbenzoate in MeOH followed by deprotection of Boc group with trifluoroacetic acid in CH_2Cl_2 and subsequent basification with Na_2CO_3 gave the *β*-phenylalanine methyl ester **5**. Amide bond between acid **4** and amine **5** using dicyclohexyl carbodiimide, hydroxy benzotriazole in methylenechloride furnished the amide **3** in 60% yield. Deprotection of acetonide group under acidic conditions (80% AcOH) gave the triol **15**. Finally, debenzylation of the triol **15** yielded the target compound **2** (scheme 3).



a) i. $NaHCO_3$, $(Boc)_2O$, dioxane:water; ii. ethyl chloroformate, TEA; iii) CH_2N_2, ether; iv) MeOH, Ag^+; b) TFA, DCM, Na_2CO_3; c) DCC, HOBt, DCM; d) 60% AcOH; e) H_2-Pd/C.

Scheme 3

Conclusions

An efficient synthesis of (2*S*,3*R*,4*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2,3,4,6-tetrahydroxyhexanoyl-β-D-phenylalanine methyl ester **2** is described from easily available building blocks (**6** and **13**). This is a common precursor for the synthesis of all the pyloricidins. This synthesis allows one to prepare various peptide analogs of the target compound for designing robust antibiotics.

Experimental Section

General Procedures. Optical rotations were measured with a JASCO DIP-360 Polarimeter at 26 ^oC and IR spectra were recorded with a Perkin Elmer FTIR spectrophotometer. ^1H NMR spectra were carried out using a Varian Gemini 200, Varian Unity 400 and Bruker Avance 300 MHz spectrophotometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for EI and VG Autospec M for FABMS mass spectrometers. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel $60F_{254}$ to a thickness of 0.25mm (Merck). Column chromatography was conducted by elution of columns with silica gel 60-120 mesh using ethyl acetate and hexane as eluents.

***tert*-Butyl-4-(1-hydroxy-(1*R*)-2-propenyl)-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (7).** To a –78 °C solution of Garner aldehyde **6** (5 g, 0.021 mol) in dry THF (100 mL) under N_2 was added vinylmagnesium bromide [prepared from vinyl bromide (6.94 g, 0.065 mol) and magnesium (1.57 g, 0.065 mol) in dry THF] over a 30 min period. The solution was stirred for 2 h at –78 °C when the TLC in hexane : ethylacetate (2:1) showed the clean formation of the product. The solution was warmed to 0 °C and partitioned between 60 mL of saturated NH_4Cl solution and 2 X 300 mL of Et_2O. The combined organic layers were washed with 100 mL of brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo and crude residue was chromatographed on silica gel using hexane:ethyl acetate (8:1) as an eluent to give 6:1 mixture of alcohols **7** and **8** as colorless oil. Alcohols **7** (4 g, 71%) and **8** (0.67 g, 12%) were further separated by column chromatography on silica gel using ethyl acetate: hexane (1:16) as an eluent (The column chromatography was performing on a glass column of length 50 cm and diameter 28 mm with gravity). $[\alpha]_D^{25}$ = -54.8° (c =2.1 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) of **7**: δ 5.93-5.72 (m, 1H), 5.42-5.15 (m, 2H), 4.30-3.80 (m, 5H (including OH)), 1.53 (s, 3H), 1.51 (s, 3H), 1.45 (s, 9H); IR (KBr): 3453, 2979, 1699, 1457, 1258, 993 cm^{-1}; FABMS: m/z 258 (M+1); Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44 Found: C, 60.12; H, 9.15; N, 5.72.

***tert*-Butyl-4-(1-hydroxy-(1*S*)-2-propenyl)-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (8).** To an ice cooled solution of alcohol **7** (4 g, 0.015 mol) in THF (120 mL) were successively added 4-nitrobenzoic acid (5.2 g, 0.031 mol), triphenylphosphine (8.34 g, 0.031 mol) then drop wise diethyl azodicarboxylate (5.4 g, 0.031 mol). The reaction was stirred for 15 min at 0 °C and 90 min at room temperature. After concentration in *vacuo*, the residue was chromatographed on silica gel (hexane : ethyl acetate 85 :15) to furnish the nitro benzoate (4.5 g, 71%) as a viscus compound. To a solution of nitro benzoate (4.5 g, 0.011 mol) in MeOH (60 mL) was added K_2CO_3 (3.1 g, 0.022 mol), after stirring the reaction mixture for 2 h at room temperature, the reaction mixture was filtered then evaporated. The residue chromatographed on silica gel column using hexane:ethyl acetate(70 : 30) gave *syn*-alcohol **8** (2.56 g, 90%, over all yield 64%). $[\alpha]_D^{25}$ = -32.4° (c =2.2 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.90-5.70 (m, 1H), 5.36 and 5.15 (s, 1H), 5.22 and 5.17 (s, 1H), 4.25 (bs, 1H, -OH), 4.18-3.80 (m, 4H), 1.57 (s, 3H), 1.52 (s, 3H), 1.45 (s, 9H); FABMS: m/z 258 (M+1).

***tert*-Butyl-4-(1-benzyloxy-(1*S*)-2-propenyl)-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (9).** To a solution of NaH (0.22 g, 0.009 mol) in dry THF (30 mL) was added alcohol **8** (2 g, 0.007 mol) at 0 °C under inert atmosphere. After stirring the reaction for 10 min at 0 °C, benzyl bromide (1.45 g, 0.0085 mol) was added and stirred for 4 h. The reaction mixture was quenched with ice and extracted with ethyl acetate (2x30 mL). Solvent was removed under *vaccuo*, crude compound was purified by silica gel column chromatography using hexane:ethyl acetate to give benzyl ether **9** (2.4 g, 90%yield). $[\alpha]_D^{25}$ = -69.65° (c =2.4 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.10 (m, 5H), 5.90-5.65 (m, 1H), 5.35-5.16 (m, 2H), 4.58 (d, *J*=13.0 Hz, 1H), 4.32 (d, *J*=13.0 Hz, 1H), 4.10-3.90 (m, 2H), 3.88-3.75 (m, 2H), 1.53 (s, 3H), 1.5-1.35 (m, 12H); IR (KBr): 3053, 2985, 1680, 1400, 1210, 723 cm^{-1}; FABMS: m/z 347 (M); Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03 Found : C, 69.08; H, 8.51; N, 4.32.

***tert*-Butyl-4-[1-benzyloxy-3-ethyloxycarbonyl-(1*S*,2E)-2-propenyl]-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (11).** *N*–Methylmorpholine *N*-oxide (1.4 g, 0.012 mol) and the olefin **9** (2.2 g, 0.006 mol) were dissolved in 30 mL of acetone:water (8:1). OsO_4 (0.02 M in Toluene, 0.4 mL) was added, and the solution was stirred for 12 h at room temperature. After cooling over an ice bath, the reaction was quenched by the addition of 15 mL of saturated $NaHSO_3$. Most of the acetone was removed by rotary evaporation, and the aqueous mixture was extracted three times with ethyl acetate (3x40 mL). Removed the solvent under reduced pressure and the compound was purified by silica gel column chromatography using hexane: ethyl acetate as an eluent gave the diol **10** (2.2 g, 91%). Sodium periodate (1.84 g, 0.008 mol) was added to a stirred solution of diol **10** (2.2 g, 0.005 mol) in 80% aq THF at 0 ^oC. After 2 h the reaction mixture was filtered and washed with ether (3x30 mL). The filtrate was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated the solvent to give aldehyde (1.8 g, 90%), which was used for the next reaction. The aldehyde (1.8 g, 0.005 mol) was dissolved in benzene (50 mL) at 0 ^oC and (carboethoxymethylene)-triphenylphosphorane (2.3 g, 0.006 mol) was added portion wise under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 4 h and benzene was evaporated under reduced pressure and purification by column chromatography gave conjugated ester **11** (2 g, 83%, over all yield 68%). $[\alpha]_D^{25}$ = -51.34^o (c =1.1 in MeOH); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.20 (m, 5H), 6.85 (d, *J*=8.0 Hz, 1H), 5.93 (d, *J*=16.0 Hz, 1H), 4.60 (d, *J*=12.8 Hz, 1H), 4.40-4.30 (m, 1H), 4.2 (q, *J*=7.6 and 14.4 Hz, 2H), 4.05-3.80 (m, 4H), 1.55 (s, 3H), 1.50 (s, 3H), 1.40 (s, 9H), 1.30 (t, *J*=6.4 Hz, 3H); FABMS: m/z 421 (M+2); Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34 Found : C, 65.94; H, 7.99; N, 3.22.

***tert*-Butyl-4-[1-benzyloxy-3-ethyloxycarbonyl-2,3-dihydroxy-(1*R*,2*R*)-propyl]-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (12).** *N*–Methylmorpholine *N*-oxide (0.83 g, 0.007 mol) and the olefin **11** (2 g, 0.0047 mol) were dissolved in 30 mL of acetone:water (8:1). OsO_4 (0.02 M in Toluene, 0.1 mL) was added, and the solution was stirred for 10 h at room temperature. After cooling over an ice bath, the reaction was quenched by the addition of 4 mL of saturated $NaHSO_3$. Most of the acetone was removed by rotary evaporation, and the aqueous mixture was extracted three times with ethyl acetate (3x10 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Crude residue was chromatographed to afford 13:1 [determined by HPLC using hypersil OD column (250x4.6 mm), MeOH: water / 70: 30, t_R = 11.4 (major), t_R = 13.7 (minor)] mixture of diols in favour of diol **12** (1.6 g, 74%). $[\alpha]_D^{25}$ = -52.7^o (c =1.2 in MeOH); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.20 (m, 5H), 4.72 (brs, 1H), 4.62 (d, *J*=8.0 Hz, 1H), 4.40-4.20 (m, 5H), 4.1 (q, *J*=4.0 and 9.6 Hz, 2H), 4.08-3.98 (m, 1H), 3.65 (t, *J*=8.0 Hz, 1H), 3.26 (d, *J*=4.0 Hz, 1H), 1.60-1.42 (m, 15H), 1.30 (t, *J*=6.40 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 174, 138, 124, 123.5, 94, 81, 75, 73, 71, 63, 62, 58, 29, 26, 25, and 14; FABMS: m/z 354 (M-Boc).

Methyl-(3S)-amino-3-phenyl-propanoate (5). To a stirred solution of compound **14** (1 g, 0.0035 mol) in 5 mL of 50 % trifluoroacetic acid in dichloromethane at 0 ^oC under inert atmosphere. Stirred the reaction mixture for 1 h and concentrated under reduced pressure. Basify the reaction mixture by adding excess of Na_2CO_3 in dichloromethane (40 mL), filter the reaction

mixture and the filtrate was concentrated under reduced pressure gave the amine **5**, which was used further without purification. Crude amine gave the satisfactory ^{1}H NMR data. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34-7.20 (m, 5H), 4.40 (t, *J*= 7.8 Hz, 1H), 3.70 (s, 3H), 3.65 (d, *J*= 7.2 Hz, 2H).

***tert*-Butyl-4-[1-benzyloxy-2,3-dihydroxy-3-[2-methyloxycarbonyl-1-phenyl-(1*S*)-ethylcarb amoyl]-(1*R*,2*R*)-propyl]-2,2-dimethyl-(4*S*)-1,3-oxazolane-3-carboxylate (3).** A mixture of ethyl ester **12** (1 g, 0.002 mol) and $LiOH.H_2O$ (0.092 g, 0.002 mol) in THF : H_2O (8:2, 10 mL) was stirred at room temperature for 2 h. Solvent was removed under *vaccuo*, residue was acidified with aq. sodium bisulphite and extracted with ethyl acetate (2x10 mL). Organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to furnish acid (0.87 g, 90%) **4**, which was used further without any purification. To a stirred mixture of acid **4** (0.6 g, 0.001 mol), amine **5** (0.25 g, 0.001 mol) and HOBt (0.25 g, 0.0018 mol) in dry DCM (10 mL) was added DCC (0.38 g, 0.0018 mol) at 0 ^{o}C under inert atmosphere. After being stirred at this temperature for 1h, the reaction mixture was warmed to room temperature and stirred for 12 h then filtered the reaction mixture and washed with DCM (2X15 mL). The filtrate was washed with 5% citric acid, saturated aq. sodium bicarbonate, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude compound was purified by silica gel column chromatography yielded (0.49 g, 60 %) the amide **3**. $[\alpha]_D^{25}$ = -1.7^o (c =1.2 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.62 (bs, 1H), 7.36-7.22 (m, 10H), 5.35 (bs, 1H), 4.70-4.55 (m, 3H), 4.30-4.16 (m, 3H), 4.10-3.90 (m, 4H), 3.60 (s, 3H), 3.65 (bs, 2H), 1.50 (m, 12H), 1.42 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): 172, 171.5, 154, 140, 138, 129, 128, 128.5, 127.5, 126, 94, 82, 80, 74, 72.5, 71.5, 64, 58, 52, 49.5, 40.5, 28.5, 27, 24.5; IR (KBr): 3343, 2979, 1699, 1657,1539 cm^{-1}; HRMS (FAB) Calcd for $C_{31}H_{42}N_2O_9$ (M^++1) 587.2968 Found : 587.2964.

(2*S*,3*R*,4*R*,5*S*)-5-(*tert*-Butyloxycarbonyl)-amino-4-benzyloxy-2,3,6-trihydroxyhexanoyl-*β*-D-phenyl alanine methyl ester (15). A solution of amide **3** (0.1 g, 0.0002) in 4 mL of 80% aq. acetic acid was stirred at room temperature for 6 h. The reaction mixture was cooled to 0 ^{o}C, diluted with chloroform (10 mL) and neutralized with saturated sodium bicarbonate solution in small portions. The organic layer was separated and aqueous layer extracted with chloroform (2x10 mL). The combined organic extracts were washed with water and brine. After drying over anhydrous Na_2SO_4. The solvent was removed under *vaccuo* and crude residue was purified by silicagel column chromatography to give ester **15** (0.055 g , 60 %). $[\alpha]_D^{25}$ = 26.19^o (c =1 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.65 (d, *J*=8.5 Hz, 1H), 7.40-7.20 (m, 10H), 5.50-5.30 (m, 2H), 4.65 (s, 2H), 4.45 (bs, 1H), 4.30-4.15 (m, 2H), 4.12-3.70 (m, 3H), 3.65 (s, 3H), 2.80 (d, *J*=8.5 Hz, 2H), 1.62 (bs, 2H, -OH), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 174.8, 173.6, 157.4, 142, 138.6, 130, 129.5, 129.2, 128.5, 128, 127.4, 84.2, 82.2, 75, 73.8, 82.4, 62.5, 54, 53, 50, 42, 29); IR (KBr): 3443, 2950, 1680, 1640,1239 cm^{-1}; HRMS (FAB) Calcd for $C_{28}H_{38}N_2O_9$ (M^+) 547.2655 Found : 547.2659.

(2*S*,3*R*,4*R*,5*S*)-5-(*tert*-Butyloxycarbonyl)-amino-2,3,4,6-tetrahydroxyhexanoyl-*β*-D-phenyl alanine methyl ester (2). A suspension of $Pd(OH)_2$ in dry methanol (5 mL)was added triol **15** (55 mg, 0.1mmol) and stirred under hydrogen atmosphere for 3 h. The reaction mixture was

filtered through a pad of celite (to remove the catalyst) washed with methanol and filtrate was concentrated under reduced pressure to give the tetrol **2** in 87% (0.04 g) yield. $[\alpha]_D^{25}$ = 36.5° (c =1 in MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.85 (d, *J*=7.7 Hz, 1H), 7.42-7.45 (m, 5H), 5.65 (d, *J*=7.6 Hz, 1H), 5.43 (q, *J*=7.6 and 15.4 Hz, 1H), 5.22 (m, 1H), 4.80 (t, *J*=11.5 Hz, 2H), 4.44-4.35 (m, 1H), 4.05-3.70 (m, 4H), 3.62 (s, 3H), 2.86 (d, *J*=7.6 Hz, 2H), 1.80 (bs, 2H, -OH), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 173.5, 172, 157.5, 140, 129, 128, 126, 81, 74.5, 72, 71.5, 61.5, 54, 53, 50, 45.5, 28.5; IR (KBr): 3400, 2979, 1710, 1680, 1450 cm^{-1}; HRMS (FAB) Calcd for $C_{21}H_{32}N_2O_9$ (M^++1) 457.2186 Found : 457.2179.

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