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Total Synthesis of Azasugar 1,4-Dideoxy-1,4-imino-D-galacitol

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A new highly stereoselective synthesis of pyrrolidine azasugar 1,4-dideoxy-1,4-imino-D-galacitol is being reported herein. The synthesis was achieved in a linear sequence and inexpensive chiral source (+)-diethyl tartarate was used as the starting material. The key step involved during the synthesis was Pd catalysed amino cyclization of alkenylamine, Bose modified Mitsunobu reaction and Sharpless asymmetric dihydroxylation.

Key Words : Azasugar, 1,4-Dideoxy-1,4-imino-D-galacitol, *E. coli K12* UDP-Gal mutase inhibitor, Pd catalysed amino cyclization

Introduction

Polyhydroxylated pyrrolidine azasugars are known to be potent glycosidase inhibitors.[1] These compounds have found various therapeutic applications in the treatment of diseases such as cancer, diabetes, AIDS, viral and bacterial infections and lysosomal storage disorder diseases such as Gaucher disease. [2] For example, the azasugar, 1,4-dideoxy-1,4-imino-L-arabinitol (LAB1) **1** is a potent and specific inihibitor of α-glucosidases[3] and inhibitor of cytopathic effect of AIDS retro virus.[2c] Its enantiomer, DAB1 **2**, a α-glycosidase inhibitor and a potential AIDS retro virus replication inhibitor.[4] The azasugar 1,4-dideoxy-1,4-imino-D-galacitol **3** acting as a weak α-glycosidase inhibitor[5] and the first azasugar to be reported specifically inhibit the mycobacterial galactan biosynthesis, probably by inhibition of the mycobacterial UDP-Gal mutase.[6] In continuation of our work on the synthesis of bioactive heterocyclic molecules[7] herein we are going to describe the synthesis of **3**[8] in a simple and linear way from (+)-diethyltartarate **6** and using Pd catalysed amino cyclization of alkenylamine as the key step.

Results and Discussion

Our synthetic plan towards 1,4-dideoxy-1,4-imino-D-galacitol **3** is outlined Scheme 1. In this designed synthetic scheme pyrrolidine derivative **4** is the key intermediate. This could be prepared by Pd catalysed amino cyclization of alkenylamine **5**. The alkenylamine **5** could be easily prepared from (+)-diethyl tartarate **6**.

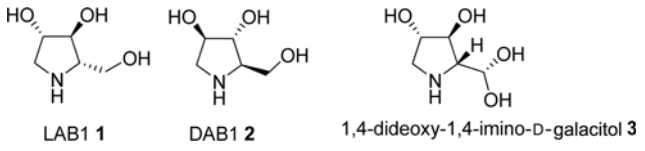
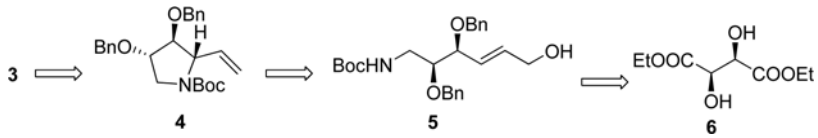
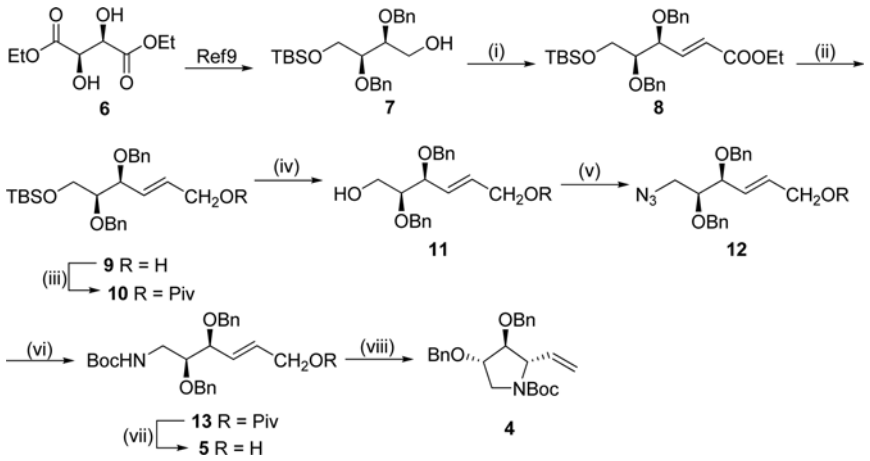


Figure 1. Polyhydroxylated pyrrolidines.

The synthesis of 1,4-dideoxy-1,4-imino-D-galacitol started with the conversion of (+)-diethyl tartarate **6** to the alcohol **7**.[9] Next, oxidation of alcohol **7** to the corresponding aldehyde was carried out under Swern oxidation condition[10] *i.e.* using oxaloyl chloride/DMSO/Et_3N at −78 °C. The aldehyde was immediately used for next step without further purification. Treatment of the crude aldehyde with Wittig reagent PPh_3=CHCOOEt in presence of a catalytic amount of benzoic acid in refluxing benzene[11] furnished selectively *E* olefin **8** (*E*:*Z* 95:5 by ^{1}H NMR analysis) with a yield of 84% over two steps (Scheme 2). The allyl ester **8** was then reduced to the corresponding allyl alcohol **9** by treating with DIBAL at −78 °C in DCM. The reaction was completed within 5 min and has to be quenched immediately otherwise it led to formation of unwanted side products. The free alcohol group of **9** was then protected as its pivaloyl ester **10** by treating with pivaloyl chloride using 4-dimethylamino pyridine as base and DCM as solvent with an excellent yield. O-Si bond cleavage of **10** was affected by the treatment with 1 M tetrabutyl ammonium fluoride solution in THF to get the free alcohol **11**. The alcohol functionality of **11** was transformed into azide functionality in a single step with high yield (77%) by applying Bose-modified Mitsunobu reaction.[12] Here alcohol **11** was treated with diphenylphosphoryl azide, triphenyl phosphine and diethyl azidocarboxylate in THF in a single-pot procedure to get the product. The azide **12** was found not to be stable and so after purification by flash chromatography was immediately reduced to amine by Staudinger reaction using PPh_3/THF/H_2O.[13] The



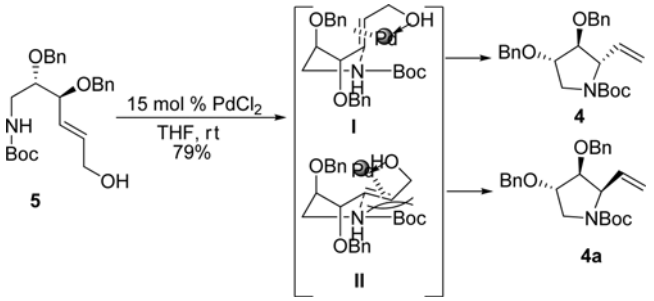
Scheme 1. Retrosynthesis of **3**.



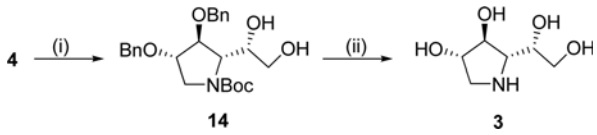
Scheme 2. Synthesis of key intermediate **4**.
Reagents and conditions: (i) (a) $(COCl)_2$, DMSO, DCM, Et_3N, −78 °C, (b) Ph_3P=CHCOOEt, C_6H_5COOH (cat.), benzene, reflux, 84% over two steps; (ii) DIBAL-H, DCM, −78 °C, 5 min, 78%; (iii) PivCl, DMAP, DCM, 0 °C-rt, 2 h, 86%; (iv) TBAF, THF, 0 °C-rt, 3 h, 88%; (v) DPPA, PPh_3, DIAD, THF, rt, 77%; (vi) (a) PPh_3, THF, H_2O, reflux, 2 h; (b) $(Boc)_2O$, Et_3N, DCM, 0 °C-rt, 1 h; 70% over two steps; (vii) DIBAL-H, −78 °C, 15 min, 76%; (viii) $PdCl_2(MeCN)_2$, THF, 4 h, 78%.

amine was not further purified and transformed to its *N*-Boc derivative **13** by treating with Boc anhydride and triethylamine and then purified by column chromatography to get pure **13**. Deprotection of pivaloyl group of **13** by treatment with DIBAL at −78 °C furnished the free alcohol **5**. It was then subjected to the key Pd catalysed amino cyclization step. On treatment with catalytic amount of $PdCl_2(MeCN)_2$ in dry THF for 4 h it underwent cyclization smoothly to give predominantly compound **4** (> 95% de) whereas its diastereomer **4a** formed only in minor amount.[14] The highly diastereoselective formation of **4** could be explained by the Scheme 3. The cyclization may proceed either *via* transition state **I** or transition state **II**. Transition state **II** would be disfavoured because of nonbonding gauche repulsion between the Boc group and the π-allyl-oxy palladium complex. So the transition state **I** will be favoured and the product **4** will form predominantly.

The terminal double bond of **4** was then subjected to Sharpless asymmetric dihydroxylation[15] to get the diol **14**. When the dihydroxylation reaction was carried out using AD-mix-α and methanesulphonamide in *t*-butanol/water 1:1 mixture the diol **14** was obtained in 84% yield and a diastereoselectivity of 79:21. To increase the diastereoselectivity chiral ligand $(DHQ)_2PHAL$ was used (2 mol %) along with AD-mix-α and methanesulphonamide and a high diastereoselectivity of > 95% was achieved. All the protecting groups of **14** were then cleaved in a single step by acidic hydrogenolysis to get **3** (Scheme 4). Spectroscopic and analytical data of the final product are in good agreement with literature values.[8]



Scheme 3. Transition state showing the selective formation of **4**.



Scheme 4. Synthesis of 1,4-dideoxy-1,4-imino-D-Galacitol **3**.
Reagents and conditions: (i) AD-mix-α, $(DHQ)_2PHAL$, methanesulphonamide, *t*-butanol/water 1:1, 16 h, 86%, (ii) H_2/Pd-C, 2 M HCl, EtOH, 12 h, 72%.

Conclusions

In conclusion, the total synthesis of pyrrolidine alkaloid 1,4-dideoxy-1,4-imino-D-galacitol was achieved in a linear sequence. Synthesis of the key intermediate, the pyrrolidine derivative was achieved with high stereoselectivity by Pd catalyzed amino cyclization reaction of alkenylamine. The main advantage of this present method of synthesis is that key pyrrolidine intermediate can lead to synthesis of many other natural and synthetic azasugars. Use of simple, stereoselective and high yielding synthetic steps make this synthesis practically feasible in comparision.

Experimental

General Methods. All the chemicals and reagents were purchased from commercial sources. Chromatographic purifications were carried out on silica 60-120 mesh as commercially available. IR spectra (neat, KBr matrix) were recorded using a Thermo Nicolet Nexus 670 FTIR spectrometer and values are given in cm^{-1}. Mass ESI data were recorded on Thermo Finnigan; HRMS (ESI) were recorded on QSTAR

XL high resolution mass spectrometer; NMR spectra were recorded on a Bruker Avance 300 MHz. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as internal standard. The optical rotations were measured on Perkin elmer 241MC and JASCO P-2000 digital polarimeters.

Preparation of (4*S*,5*S*,*E*)-Ethyl 4,5-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)hex-2-enoate (8): To a solution of oxaloyl chloride (3.7 mL, 43.27 mmol, 1.5 equ.) in dry DCM (30 mL) was added drop wise a solution of DMSO (4.6 mL, 64.24 mmol, 2.24 equ.) in DCM (15 mL) at −78 °C. After 15 minute a solution of alcohol **7** (12.0 g, 28.85 mmol, 1.0 equ.) in DCM (30 mL) was added to the reaction mixture and allowed to stir for further 2 h at the same temperature. Then triethyl amine (16.2 mL, 115.4 mmol, 4.0 equ.) was injected at that temperature and the reaction mixture was allowed to reach to 0 °C, when it was quenched upon addition of aqueous ammonium chloride solution (20 mL). The reaction mixture was then extracted with DCM (3 × 40 mL) and combined organic layers were then washed with brine (50 mL) and dried over Na_2SO_4 and concentrated under vacuum to get the crude aldehyde as yellow oil which was immediately used for next step without further purification.

To a refluxing benzene solution of PPh_3=CHCOOEt (12.04 g, 34.62 mmol, 1.2 equ.) was added a benzene solution of the crude aldehyde drop wise with constant stirring. After 5 minute the reaction mixture was taken out of the oil bath and allowed to cool to rt. The solvent was evaporated out and the resulting residue was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/ hexane 1:10) to afford the pure allyl ester **8** as colorless oil (11.4 g, 84%). $[\alpha]_D^{25}$ +13.4 (*c* 1.0, $CHCl_3$); IR: 2937, 2876, 1733, 1665, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (m, 10H, 2 Ph), 6.99 (dd, *J* = 15.8, 5.6 Hz, 1H, H-3), 6.10 (d, *J* = 15.8 Hz, 1H, H-2), 4.76-4.64 (m, 3H, CH_2Ph), 4.48 (d, *J* = 10.6 Hz, 1H, CH_2Ph), 4.27 (q, *J* = 6.9 Hz, 2H, $COOC\underline{H_2}$), 4.23-4.17 (m, 1H, H-6), 3.82 (dd, *J* = 10.8, 3.9 Hz, 1H, H-6), 3.67 (dd, *J* = 10.8, 5.9 Hz, 1H, H-4), 3.60-3.55 (m, 1H, H-5), 1.38 (t, *J* = 6.9 Hz, 3H, $COOCH_2\underline{CH_3}$), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 145.2, 138.5, 137.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 122.8, 81.5, 78.3, 73.4, 71.9, 62.9, 60.2, 26.1, 18.4, 14.5, −5.2; MS (ESI): *m/z* 507 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{28}H_{40}O_5SiNa$: $[M+Na]^+$ 507.2543, found: 507.2549.

Preparation of (4*S*,5*S*,*E*)-4,5-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)hex-2-en-1-ol (9): To a solution of the allyl ester **8** (11.0 g, 24.46 mmol, 1.0 equ.) in dry DCM was added a solution of DIBAL 25 wt % in toluene (30.6 mL, 53.81 mmol, 2.2 equ.) over a period of 15 minute with constant stirring at −78 °C. The reaction was completed within 5 min and was immediately quenched by addition of aqueous ammonium chloride solution and allowed to stir at rt for 2 h. It was then filtered, the residue was washed well with DCM and the combine filtrates were dried over Na_2SO_4 and concentrated under vacuum to get the crude allyl alcohol **9** which was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:7) to afford the pure product as yellow oil (8.43 g, 78%). $[\alpha]_D^{25}$ +23.8 (*c* 1.0, $CHCl_3$); IR: 3423, 2935, 1442, 1367, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 10H, 2 Ph), 5.80 (dt, *J* = 15.7, 5.1 Hz, 1H, H-3), 5.65 (dd, *J* = 15.8, 7.1 Hz, 1H, H-2), 4.72-4.53 (m, 3H, CH_2Ph), 4.36 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.07 (d, *J* = 4.9 Hz, 2H, H-1), 3.97-3.90 (m, 1H, H-6), 3.76 (dd, *J* = 10.6, 4.1 Hz, 1H, H-6), 3.64 (dd, *J* = 10.6, 6.0 Hz, 1H, H-4), 3.46 (dd, *J* = 10.0, 4.7 Hz, 1H, H-5), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.025 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.5, 133.1, 128.4, 128.23, 128.18, 128.06, 127.7, 127.47, 127.42, 82.2, 79.2, 73.5, 70.8, 63.2, 62.7, 26.1, 18.4, −5.2; MS (ESI): *m/z* 465 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{26}H_{38}O_4SiNa$: $[M+Na]^+$ 465.2437, found: 465.2431.

Preparation of (4*S*,5*S*,*E*)-4,5-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-1pivaloylhex-2-ene (10): The allyl alcohol **9** (8.0 g, 18.10 mmol) was dissolved in dry DCM (50 mL) and cooled to 0 °C. To it was then added 4-dimethylamino pyridine (2.43 g, 19.90 mmol, 1.1 equ.) followed by pivaloyl chloride (2.45 mL, 19.90 mmol, 1.1 equ.). The reaction mixture was then allowed to stir at rt for 4 h. It was then quenched by addition of water (5 mL), DCM layer was separated out, the aqueous layer was extracted with DCM (20 mL × 3), dried over Na_2SO_4 and concentrated under vacuum to get the crude product which was purified by columm chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:20) to afford the pure product **10** as yellow oil (8.18 g, 86%). $[\alpha]_D^{25}$ +15.2 (*c* 1.0, $CHCl_3$); IR: 2952, 1744, 1593, 1486, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 10H, 2 Ph), 5.80- 5.74 (m, 2H, H-3, H-2), 4.73-4.59 (m, 3H, benzyl protons), 4.58-4.53 (m, 2H, 2 H-1), 4.36 (d, *J* = 11.8 Hz, 1H, benzyl proton), 3.99-3.93 (m, 1H, H-6), 3.75 (dd, *J* = 10.6, 4.1 Hz, 1H, H-6), 3.61 (dd, *J* = 10.6, 6.0 Hz, 1H, H-4), 3.50-3.42 (m, 1H, H-5), 1.21 (s, 9H, pivaloyl protons), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.3, 131.1, 128.2, 128.1, 127.9, 127.6, 127.4, 82.1, 78.8, 73.5, 70.8, 64.0, 63.0, 27.2, 26.5, 25.9, −5.5; MS (ESI): *m/z* 549 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{31}H_{46}O_5SiNa$: $[M+Na]^+$ 549.7692, found: 549.7692.

Preparation of (4*S*,5*S*,*E*)-4,5-Bis(benzyloxy)-6-hydroxy-1-pivaloyloxyhex-2-ene (11): To a solution of the TBS protected alcohol **10** (8 g, 15.20 mmol, 1.0 equ.) in THF (50 mL) was a added a solution of tetrabutylammonim fluoride 1 M in THF (18.2 mL, 18.2 mmol, 1.2 equ.) drop wise with constant stirring at 0 °C. The resulting solution was then stirred at rt for 5 h when TLC showed complete consumption of the starting material. It was then quenched with addition of water at 0 °C and extracted with ethyl acetate (40 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to get the crude alcohol which was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:4) to afford the pure product **11** as yellow oil (5.51 g, 88%). $[\alpha]_D^{25}$ +17.6 (*c* 1.0, $CHCl_3$); IR: 3470, 2918, 1741, 1654, 1462, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.22 (m,

10H, 2 Ph), 5.82 (dt, *J* = 15.8, 5.3Hz, 1H, H-3), 5.71 (dd, *J* = 15.8, 6.9 Hz, 1H, H-2), 4.77-4.68 (m, 2H, 2 H-1), 4.65-4.54 (m, 3H, benzyl prptons), 4.37 (d, *J* = 11.8 Hz, 1H, benzyl proton), 4.02-3.95 (m, 1H, H-6), 3.70-3.46 (m, 3H, H-6, H-4, H-5), 1.88 (brs, 1H, OH), 1.21 (s, 9H, pivaloyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 138.2, 138.0, 130.0, 129.0, 128.5, 128.0, 127.9, 127.8, 81.0, 80.0, 73.4, 70.8, 63.8, 62.0, 27.2; MS (ESI): *m/z* 435 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{31}H_{46}O_5Na$: $[M+Na]^+$ 435.2147, found: 435.2144.

Preparation of (4*S*,5*S*,*E*)-6-Azido-4,5-bis(benzyloxy)-1-pivaloyloxyhex-2-ene (12): To a solution of alcohol **11** (5.51 g, 13.35 mmol) and triphenylphophine (8.4 g, 32.03 mmol, 2.4 equ.) in dry THF was added diisopropylazodicarboxylate (6.3 mL, 32.03 mmol, 2.4 equ.) and diphenylphosphoryl azide (8.8 g, 32.03 mmol, 2.4 equ.) drop wise at 0 °C. The reaction mixture was then stirred at rt for 2 h when TLC showed complete consumption of the starting material. The volatiles were removed under reduced pressure and the resulting solid residue was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:15) to afford the pure product **12** as colourless oil (4.43 g, 77%). $[\alpha]_D^{25}$ +14.8 (*c* 1.0, $CHCl_3$); IR: 2974, 2112, 1736, 1447, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.42 (m, 10H, 2 Ph), 5.81 (dt, *J* = 15.8, 5.5 Hz, 1H, H-3), 5.68 (dd, *J* = 16.0, 6.8 Hz, 1H, H-2), 4.68-4.52 (m, 5H, 3 benzyl protons, 2 H-1), 4.36 (d, *J* = 11.8 Hz, 1H, benzyl proton), 3.65-3.55 (m, 1H, H-4), 3.40-3.20 (m, 3H, H-5, 2 H-6), 1.20 (s, 9H, pivaloyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 130.0, 129.6, 129.0, 128.3, 128.0, 127.8, 126.1, 120.2, 120.1, 80.1, 78.9, 73.5, 70.8, 63.6, 51.5, 51.0, 27.1; Mass (ESI)**:** *m/z* 460 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{25}H_{31}N_3O_4Na$: $[M+Na]^+$ 460.2212, found: 460.2217.

Preparation of (4*S*,5*S*,*E*)-4,5-Bis(benzyloxy)-6-(*tert*-butoxycarbonylamino)pivaloyloxyhex-2-ene (13): A solution of the azide **12** (4.43 g, 10.14 mmol, 1.0 equ.) and triphenylphosphine (8.0 g, 30.41 mmol, 3.0 equ.) in THF (30 mL) was refluxed for 1 h before water (1 mL) was added and the reaction mixture was refluxed for another 1 h, cooled to rt and diluted with ethyl acetate (50 mL). This solution was washed with 5% $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried (Na_2SO_4) and concentrated under vacuum to get the crude amine which was used for next step without further purification.

The crude amine was dissolved in DCM (30 mL) and cooled to 0 °C. To it was then added triethylamine (1.7 mL, 12.16 mmol, 1.2 equ.) followed by $(Boc)_2O$ (2.7 mL, 12.16 mmol, 1.2 equ.) and the resulting solution was stirred at rt for 4 h. The reaction mixture was then quenched with water (10 mL) and diluted with DCM (50 mL). The organic layer was separated out, dried over Na_2SO_4 and concentrated under vacuum to get the crude alcohol which was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:5) to afford the pure product **13** as viscous liquid (3.62 g, 70%). $[\alpha]_D^{25}$ +24.8 (*c* 1.0, $CHCl_3$); IR: 3239, 1741, 1698, 1445, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 10H, 2 Ph), 5.81 (dt, *J* = 15.6, 5.5 Hz, 1H, H-3), 5.73 (dd, *J* = 15.6, 6.2 Hz, 1H, H-2), 4.72-4.56 (m, 5H, 3 benzyl protons, 2 H-1), 4.36 (d, *J* = 11.8 Hz, 1H, benzyl proton), 3.92-3.87 (m, 1H, H-4), 3.56-3.49 (m, 1H, H-5), 3.38-3.27 (m, 1H, H-6), 3.15-3.06 (m, 1H, H-6), 1.40 (s, 9H, Boc protons), 1.21 (s, 9H, pivaloyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 130.1, 128.8, 128.3, 128.0, 127.8, 127.7, 79.9, 79.3, 73.2, 70.6, 63.7, 40.9, 38.7, 28.4, 27.3; Mass (ESI): *m/z* 534 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{30}H_{41}NO_6Na$: $[M+Na]^+$ 534.2832, found: 534.2828.

Preparation of (4S,5S,*E*)-4,5-Bis(benzyloxy)-6-(*tert*-butoxycarbonylamino)-1-pivaloylhex-2-ene (5): To a solution of the alcohol **13** (3.62 g, 7.1 mmol, 1.0 equ.) in dry DCM was added a solution of DIBAL 25 wt % in toluene (8.8 mL, 15.62 mmol, 2.2 equ.) over a period of 10 min at -78 °C and allowed to stir at that temperature for further 15 min. The reaction mixture was then quenched by addition of aqueous ammonium chloride solution (10 mL) and allowed to stir at rt for 3 h. It was then filtered, the residue was washed well with DCM and the combine filtrates were dried over Na_2SO_4 and concentrated under vacuum to get the crude product which was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:10) to afford the pure amino alcohol **86** as yellow oil (2.30 g, 76%). $[\alpha]_D^{25}$ +21.3 (*c* 1.0, $CHCl_3$); IR: 3473, 3482, 1701, 1678, 1445, 1131 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 10H, 2 Ph), 5.85 (dt, *J* = 15.3, 5.4 Hz, 1H, H-3), 5.63 (dd, *J* = 15.5, 7.8 Hz, 1H, H-2), 4.81-4.57 (m, 4H, 3 benzyl protons, H-1), 4.36 (d, *J* = 11.8 Hz, 1H, benzyl proton), 4.12 (d, *J* = 5.0 Hz, 1H, H-1), 3.95-3.88 (m, 1H, H-4), 3.59-3.50 (m, 1H, H-5), 3.35-3.12 (m, 2H, 2 H-6), 1.41 (s, 9H, Boc protons); Mass (ESI): *m/z* 450 $[M+Na]^+$. HRMS (ESI): *m/z* Calcd for $C_{25}H_{33}NO_5Na$: $[M+Na]^+$ 450.2256, found: 450.2256.

Preparation of (2*S*,3*S*,4*S*)-1-(*tert*-Butyloxycarbonyl)-3,4-bis(benzyloxy)-2-ethenylpyrrolidine (4): To an ice cooled solution of the amino alcohol **5** (2.3 g, 5.38 mmol, 1.0 equ.) in dry THF (20 mL) was added catalytic amount of $PdCl_2(MeCN)_2$ (140 mg, 10 mol %) and stirred at rt for 4 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (30 mL × 3). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum to get the cyclised product which was purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:10) to afford the pure product as yellow oil (1.72 g, 78%). $[\alpha]_D^{25}$ −11.4 (*c* 1.0, $CHCl_3$); IR: 3019, 1696, 1634, 1447, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 10H, 2 Ph), 5.88-5.75 (m, 1H, CH_2=C<u>H</u>), 5.28-5.02 (m, 2H, C<u>H$_2$</u>=CH), 4.67-4.40 (m, 4H, benzyl protons), 4.21-4.07 (m, 1H, H-2), 4.00-3.94 (m, 1H, H-3), 3.86-3.81 (m, 1H, H-2), 3.78-3.63 (m, 1H, H-5), 3.51-3.42 (m, 1H, H-5), 1.43 (s, 9H, Boc protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 137.1, 136.8, 128.4, 127.8, 127.7, 127.6, 127.5, 115.8, 115.6, 79.6, 71.6, 71.3, 65.3, 28.4; Mass (ESI): *m/z* 432 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd for $C_{25}H_{31}NO_4Na$: $[M+Na]^+$ 432.2151, found: 432.2157.

Preparation of (2*S*,3*S*,4*S*)-1-(*tert*-Butyloxycarbonyl)-2-

((*S*)-1,2-dihydroxyethyl)-3,4-bis(benzyloxy)-pyrrolidine using AD-mix α (14): To the compound **4** (0.11 g, 0.25 mmol, 1.0 equ.) dissolved in *t*-BuOH/water 1:1 (3 mL) was added AD-mix-α (0.42 g, 0.3 mmol, 1.2 equ.), $(DHQ)_2PHAL$ (4 mg, 0.005 mmol, 2 mol %) and methanesulphonamide (0.70 g, 0.75 mmol, 3.0 equ.) and stirred for 12 h at rt. The reaction mixture was then quenched with aqueous sodium sulfite solution (5 mL) and extracted with ethyl acetate (10 mL × 3). The orgnic layer was then washed with brine, dried over Na_2SO_4 and concentrated under vacuum and purified by column chromatography on silica gel 60-120 mesh (eluent ethyl acetate/hexane 1:5 followed by 1:1) to afford the pure diol **14** as viscous oil (90.0 mg, 84%). $[\alpha]_D^{25}$ +21.4 (*c* 1.0, $CHCl_3$); IR: 3443, 2873, 1689, 1378, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (m, 10H, 2 Ph), 4.65 (d, *J* = 12.1 Hz, 1H, benzyl proton), 4.53 (dd, *J* = 6.0 Hz, 2H, benzyl protons), 4.43 (dd, *J* = 11.3 Hz, 1H, benzyl proton), 4.36-4.29 (m, 2H, C<u>H</u>OHCH$_2$OH and 1 CHOHC<u>H$_2$</u>OH), 4.02 (d, *J* = 4.5 Hz, 1H, 1 CHOHC<u>H$_2$</u>OH), 3.90 (d, *J* = 9.8 Hz, 1H, H-2), 3.80-3.51 (m, 3H, H-5, H-4, H-3), 3.43 (d, *J* = 12.1 Hz, 1H, H-5), 2.77 (br s, 1H, OH), 1.46 (s, 9H, Boc protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 137.7, 137.2, 128.45, 128.40, 127.85, 127.75, 127.68, 82.0, 81.3, 80.8, 71.2, 71.1, 70.6, 63.8, 62.3, 52.3, 28.3; Mass (ESI): *m/z* 444 $[M+H]^+$; HRMS (ESI): *m/z* Calcd for $C_{25}H_{34}NO_6$: $[M+H]^+$ 444.2386, found: 444.2382. For minor isomer $[\alpha]_D^{25}$ +16.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 10H, 2 Ph), 4.64 (d, *J* = 12.1 Hz, 1H, benzyl proton), 4.56-4.45 (m, 2H, benzyl protons), 4.41-4.34 (m, 1H, benzyl proton), 4.31-4.27 (m, 1H, C<u>H</u>OHCH$_2$OH), 3.95 (d, *J* = 4.5 Hz, 1H, 1 CHOHC<u>H$_2$</u>OH), 3.83 (d, *J* = 9.8 Hz, 1H, 1 CHOHC<u>H$_2$</u>OH), 3.74-3.57 (m, 3H, H-2, H-3, H-4), 3.56-3.45 (m, 1H, H-5), 3.38 (d, *J* = 12.1 Hz, 1H, H-5), 1.47 (s, 9H, Boc protons).

Preparation of 1,4-Dideoxy-1,4-imino-D-Galacitol (3): To a solution of **14** (50 mg) in 3 M HCl in ethanol (3 mL) was added Pd/C 10% and the heterogenous mixture was stirred vigorously for 24 h under hydrogen atmosphere. The solution was filtered through celite and the residue was washed with ethanol. The filtrate was then concentrated under vaccum to syrup and was then washed with chloroform. Then ethanol (10 mL) was added again and evaporated. Evaporation of ethanol solution was repeated for four times to get hydrochloride salt as white solid. Free base oil **3** (12 mg, 72%) was obtained by passing an aqueous solution of the hydrochloride salt through a columm of Amberlite IRA-400 (OH^-). The column was eluted with methanol, then water followed by 2% ammonium hydroxide. $[\alpha]_D^{25}$ +2.9 (c, 1.0, H_2O), IR: 3457, 3029, 1714, 1672, 1195 cm^{-1}, ^1H NMR (300 MHz, D_2O) δ 4.05-3.99 (m, 1H, H-4), 3.79 (dd, *J* = 6.2, 3.9 Hz, 1H, H-3), 3.71-3.62 (m, 1H, C<u>H</u>OHCH$_2$OH), 3.51-3.45 (m, 1H, 1 CHOHC<u>H$_2$</u>OH), 3.40-3.33 (m, 1H, 1 CHOHC<u>H$_2$</u>OH), 3.06 (dd, *J* = 12.0, 5.6 Hz, 1H, H-5), 2.80 (d, *J* = 8.4 Hz, 1H, H-2), 2.72 (m, 1H, H-5). ^{13}C NMR (75 MHz, D_2O) δ 79.4, 77.2, 71.3, 66.4, 64.4, 50.9.

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