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A Stereoselective Synthesis of an Imino Glycal: Application in the Synthesis of (–)-1-*epi*-Adenophorine and a Homoiminosugar

Ande Chennaiah,[a] Amit Dahiya,[a]† Sateesh Dubbu[a] and Yashwant D. Vankar*[a]

Dedication ((optional))

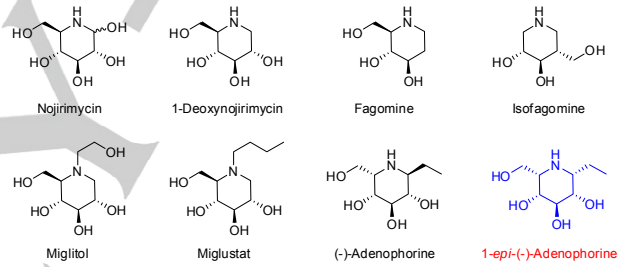
Abstract: A concise stereoselective synthesis of an imino glycal is described in 8 steps starting from 1,2-anhydro-3,4,6-tri-O-benzyl-D-glucopyranose. The utility of the imino glycal has been demonstrated in synthesis of (–)-1-*epi*-adenophorine and a homoiminosugar as a glycosidase inhibitor. The important features of the developed route include high yields, high stereoselectivity, and application in the synthesis of other iminosugars. Additionally, a new synthon 2-nitro-imino glycal has also been synthesized which could act as valuable synthon in carbohydrate chemistry.

Introduction

Glycals are carbohydrate derived cyclic enol ethers having a double bond between C-1 and C-2 carbons. They have been recognized as excellent synthons in synthetic organic chemistry, in general, and in carbohydrate chemistry, in particular. For example, (i) 3,4,6-tri-O-benzyl D-glycals can act as glycosyl donors and thus could be used in the synthesis of oligosaccharides and other enantiomerically pure organic molecules,[1] (ii) a variety of nucleophiles can be introduced at C-1 position of a glycal through S_N1' reaction which possess a good leaving group at C-3 carbon with migration of the double bond in a reaction called the Ferrier reaction.[2] (iii) glycals allow a variety of functionalizations at C-2 to lead to highly useful synthons such as 2-nitro-,[3] 2-halo,[4] 2-formyl,[5] 2-sulfonyl-,[6] and 2-acetoxy glycals.[7] These synthons have been widely used in the synthesis of biologically active compounds like iminosugars, C-, O-, and N-glycosides, and N-glycopeptides.[8] Therefore, it would be interesting to study the reactivity of imino glycals which are molecules with the ring oxygen in glycals replaced by nitrogen.

Iminosugars are of great interest because they are known to act as glycosidase and glycosyl tansferase inhibitors influencing many biological processes.[9] A number of important iminosugars are piperidine derivatives (Figure 1) and they exhibit enormous therapeutic potential in many diseases such as diabetes,[10] cancer[11] and lysosomal storage disorders.[12] Thus, for example,[13] 1-deoxynojirimycin acts as a potent α-glucosidase inhibitor[14] and its derivative N-hydroxyethyl-1-deoxynojirimycin[15] (miglitol) is used against type II diabetes, and N-butyl-1-deoxynojirimycin[16] (miglustat) is useful against Gaucher's disease by inhibiting glucosyl ceramide synthase (a glycosyltransferase). In this context, adenophorine and its analogs are a group of structurally diverse iminosugar C-glycosides which were isolated by Asano and co-workers in 2000.[17] (–)-Adenophorine contains an ethyl group at the anomeric centre and shows α-glucosidase inhibitor activity with IC_{50} value being 32 μM. As a result, a few reports have appeared in the literature for the synthesis of adenophorine and its analogs.[18]

Figure 1: Selected examples of biologically active iminosugars



In view of the importance of iminosugars (vide supra), we surmised that imino glycals, having an easily exploitable double bond, could serve as good precursors for their preparation. Despite their importance, it is surprising that only a few synthesis of imino glycals have been reported in the literature. The only notable work is due to Shipman and co-workers[19] who reported the synthesis of a few imino glycals and their derivatives such as 2-benzyloxy and 2-bromo-imino glycals and showed their utility in the synthesis of (+)-fagomine, deoxymannojirimycin analogues, and (+)-deoxoprosophylline. They first synthesized tri-O-benzyl imino glucal in 8 steps and later also synthesized tri-O-acetyl imino glucal in 11 steps in an overall yields of 19% and 10% respectively from 2,4,6-tri-O-benzyl glucal as a starting material. On the other hand, a non-carbohydrate approach for the synthesis of imino glycals was reported by Commins et al.[20] starting from substituted pyridine derivatives and utilized in the synthesis of 1-deoxynojirimycins and (+)-deoxoprosopinine.

In continuation of our interest in synthesizing structurally diverse sugar derivatives as glycosidase inhibitors,[21] we herein wish to report a stereoselective synthesis of an imino glycal. Further, we also report on the utility of the imino glycal in the synthesis of (–)-1-*epi*-adenophorine, and a homoiminosugar and report its glycosidase inhibition activity.

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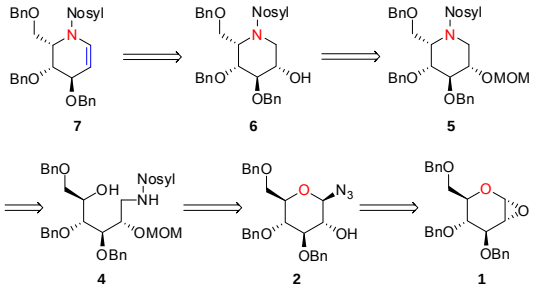
Results and Discussion

It was envisaged that the synthesis of imino glycal **7** (Scheme 1) could be achieved by simple elimination of the hydroxyl group in compound **6**, which could be prepared by the MOM deprotection of the piperidine derivative **5** with TFA. This piperidine derivative **5** was planned to be constructed from compound **4** via an intramolecular Mitsunobu reaction. The amino alcohol **4** could be procured from compound **2** by reducing the anomeric azide moiety with $LiAlH_4$, followed by protection of the free amine with nosyl chloride. Compound **2**, in turn, can be easily derived by opening of the glucal derived epoxide **1** with NaN_3.

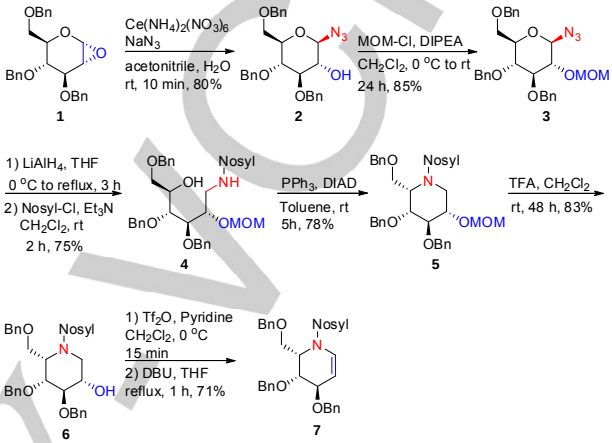
Scheme 1: Retrosynthesis of imino glycal **7**



Our synthesis emanated from 1,2-anhydro-3,4,6-tri-O-benzyl-D-glucopyranose **1**, which was converted into 2-hydroxy azide **2** by reacting with sodium azide in the presence of ceric ammonium nitrate (CAN) by following a protocol developed by our group.[22] Protection of the hydroxyl group in compound **2** with MOM-Cl in presence of N,N-diisopropylethylamine (DIPEA) yielded compound **3** in 85% yield. Reduction of the azide moiety along with the ring opening of compound **3** was accomplished with $LiAlH_4$ in THF to lead to the corresponding amino alcohol. The resulting crude amino alcohol was reacted with nosyl chloride to get the nosyl protected amine **4** whose spectral data (see the supporting information)[23] confirmed the structure. In order to retain the N-nosyl group for synthetic manipulations, we carried out an intramolecular Mitsunobu reaction with triphenylphosphine and DIAD to get the cyclized product **5** in 78% yield. The structures of the products were confirmed by spectral analysis.[23] Appearance of $[M + H]^+$ peak at 663.2372 (calculated 663.2376) in its high resolution mass spectrum, along with the other spectral data,[23] confirmed that cyclization had occurred.

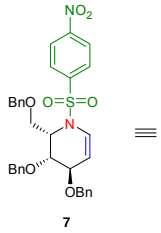
It was expected that the synthon **5** could be easily converted into imino glycal by elimination of the hydroxy group. For this purpose, first deprotection of the MOM group was carried out using trifluroacetic acid (TFA) to get the hydroxyl compound **6** in 83% yield. The hydroxyl group was then reacted with triflic anhydride and pyridine at 0 °C to form the corresponding triflate which was used, without purification, for the next step. The desired target molecule **7** was obtained by elimination of the triflate group using DBU in THF at 60 °C. The structure of the product **7** was confirmed by spectral analysis[23] including its high resolution mass spectrum which showed the appearance of $[M + NH4]^+$ peak at 618.2271 (calculated 618.2274). Further, for proving the stereochemistry at C-5, COSY and NOE experiments were carried out. In NOE experiments, upon irradiation of the signal for H-3 at δ 4.12 no enhancement of H-5 at δ 4.24 was observed indicating that H-3 and H-5 protons are likely to be trans oriented.

Scheme 2: Stereoselective synthesis of imino glycal **7**



Additionally, the imino glycal **7** (Scheme 2) was obtained as a crystalline compound, and its X-ray crystallographic analysis (Figure 2, CCDC: 1849471) confirmed the stereochemistry. Accordingly, the benzyloxymethyl group at C-5 carbon is α-oriented and the absolute stereochemistry at this centre (i.e. C-5) is 5S. Thus, the stereoselective synthesis of the imino glycal **7** was achieved successfully.

Figure 2: X-Ray structure of imino glycal **7**



X-ray ORTEP diagram showing 30% probability thermal ellipsoids of compound **7** (CCDC 1849471)

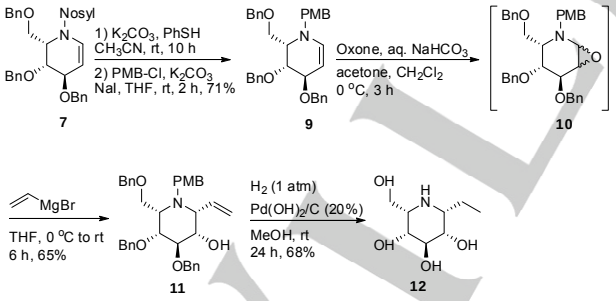
Having developed a simple and efficient method for the preparation of imino glycal **7**, we wished to utilize it in the synthesis of adenophorine analogue and an aminosugar. Initially, we considered converting **7** into the corresponding 2-nitroglycal **8** on which the Michael addition of vinyl magnesium bromide was envisaged to be easily carried out. This could be followed by converting the nitro group into a carbonyl group whose reduction to a hydroxyl group in either stereochemical orientation could pave way to adenophorine analogues. In addition, the nitro group could also be reduced to an amino functionality and thus another iminosugar can be procured. We have been actively involved in the synthesis as well as functionalization of 2-nitroglycals[3a], [24] and thus we carried out

the nitration of **7** to get the 2-nitro-imino glycal **8** (Scheme 3) using standard nitration condition[25] used for the conversion glycals into 2-nitroglycals. Unfortunately, however, the reaction of **8** with vinyl magnesium bromide under varying temperatures was not clean and thus we could not proceed with compound **8**. However, we believe that compound **8** could serve as an important synthon in organic chemistry, and in particular in carbohydrate chemistry.

Scheme 3: Conversion of imino glycal into 2-nitro-imino glycal

(–)-1-*epi*-adenophorine is an analogue of adenophorine[18b] and shows α-L-fucosidase inhibitor activity (IC_{50} = 208 μM).[18c] We considered that with the 'S' configuration at C-5, the imino glycal **7** is a perfectly suitable synthon for the synthesis of (–)-1-*epi*-adenophorine. Introduction of an ethyl group onto imino glycals has been reported by a Lewis acid mediated addition of diethyl zinc[19c] leading to a 2,3-unsaturated iminosugar via Ferrier rearrangement. However, since (–)-1-*epi*-adenophorine is a 2-hydroxy iminosugar we thought to perform epoxidation of imino glycal **7**, followed by its opening to introduce an ethyl group at C1. Thus, imino glycal **7** was subjected to epoxidation under known reaction conditions using Oxone® (Scheme 4).[26] However, the reaction was not successful and the starting material was recovered. We envisaged that the imino glycal with an electron-donating group on the ring nitrogen could be more reactive than the one with an electron withdrawing nosyl group and thus may undergo epoxidation. Accordingly, we changed

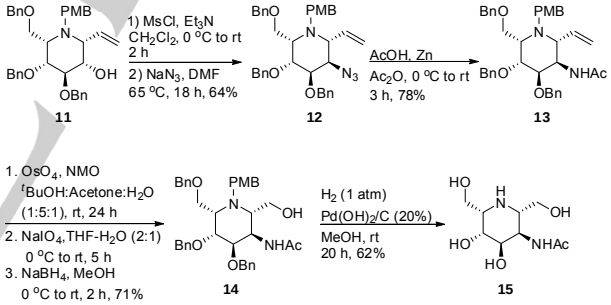
Scheme 4: Synthesis of (–)-1-*epi*-adenophorine **12**



the protecting group on the ring nitrogen from nosyl to *p*-methoxy benzyl (PMB) group to obtain **9** which smoothly underwent epoxidation to form the epoxide **10** which was rather very unstable and could not be purified. Hence crude compound **9** was reacted with vinyl magenisum bromide to afford compound **11** as a single diastereomer. The stereochemistry at the newly generated centres of compound **11** was confirmed by spectral analysis including COSY and NOE studies.[23] Further, complete debenzylation as well as hydrogenation of the double bond using $Pd(OH)_2$/C (20%) under H_2 (1 atm) led to (–)-1-*epi*-adenophorine **12** in 68% yield whose structure was confirmed by spectral analysis.[23] The spectroscopic data of **12** were also in good agreement with the reported data.[18c]

Recently, Blériot and co-workers reported the synthesis of 1,2-cis-homoiminosugars derived from GlcNAc and GalNAc by employing skeletal rearrangement on an azepane precursor.[27] One of the 1,2-cis-homoiminosugars (α-D-GalNAc-configured) showed glycosidase inhibitory activity with IC_{50} value being 1.1 μM against α-*N*-acetylgalactosaminidase (chicken liver). Thus, we expected that functionalization of compound **11** could lead to a similar type of homoiminosugar which could also act as a glycosidase inhibitor. Therefore, in order to introduce an amino group at C-2 position, compound **11** (Scheme 5) was subjected to mesylation followed by replacement of a mesylate by an azido group with NaN_3 to furnish the product **12** in 64% yield with inversion of configuration. The azide group in compound **12** was reduced directly to corresponding acetamido product **13** by following a literature procedure.[28] Further, the piperidine derivative **13** was converted into compound **14** upon sequential OsO_4/NMO mediated dihydroxylation, diol cleavage to the corresponding aldehyde using $NaIO_4$ and reduction with $NaBH_4$ in 71% overall yield in three steps. Treatment of compound **14** with 20% $Pd(OH)_2$/C in methanol under 1 atm of hydrogen for 20 h furnished the target product **15** in 62% yield.

Scheme 5: Synthesis of homoiminosugar **15**



The inhibitory activity (IC_{50} in μM) of compound **15** was checked against commercially available α-galactosidase (coffee beans), β-galactosidase (bovine liver), α-glucosidase (rice) and β-glucosidase (almonds).[29] It was found that compound **15** was active only against α-galactosidase (coffee beans) with IC_{50}= 125 μM. It is expected that structural modifications of **15** could lead to improved/or altered inhibition activity.

Conclusions

In conclusion, a new short and efficient route for the synthesis of an imino glycal from 1,2-anhydro-3,4,6-tri-O-benzyl-D-glucopyranose is described in 23% overall yield in eight steps. The application of imino glycal is shown in a rapid synthesis of (–)-1-*epi*-adenophorine, which is an α-L-fucosidase inhibitor. Further, a homoiminosugar is also synthesized which shows moderate selective glycosidase inhibitor activity against α-

galactosidase (coffee beans). Imino glycal was also converted into a 2-nitro-imino glycal, which may find application in carbohydrate chemistry. Moreover, synthesized imino glycal offers possible extensions to synthesize a large number of biologically important iminosugars. Further work on exploring the utility of imino glycal and related compounds is ongoing and will be reported in due course.

Experimental Section

General procedures: All experiments were done in an oven-dried apparatus and under N_2 atmosphere in dry solvents. Commercial grade solvents were dried by known methods, and dry solvents were stored over 4 Å molecular sieves. IR spectra were recorded on FT-IR spectrometer (KBr) and are expressed in cm^{-1}. High resolution mass spectra were measured by Q-TOF using electrospray ionization (ESI) method. ^1H (500 MHz or 400 MHz) and ^{13}C (125 MHz or 100 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O as solvents. Coupling constants are reported and expressed in Hertz, splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), q (quartet), m (multiplet). Rotation values were recorded on AUTOPOL II polarimeter at 28 °C in DCM and D_2O. Thin-layer chromatography (TLC) plates were prepared by using silica gel on microscopic slides, and visualization of spots was done by exposure to iodine or by spraying 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100−200 Mesh) using hexane and ethyl acetate as eluents.

(2R,3R,4R,5R,6R)-2-azido-4,5-bis(benzyloxy)-6-((benzyloxy)methyl) tetrahydro-2H-pyran-3-ol (2): Compound **2** was prepared from **1** (2 g, 4.62 mmol) using a known literature procedure**1** in 80% yield (1.75 g) as a white solid.[22] ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.23 (m, 13H), 7.19–7.12 (m, 2H), 4.82 (dd, J = 20.0, 5.7 Hz, 3H), 4.61 (d, J = 12.2 Hz, 1H), 4.51 (ddd, J = 14.8, 11.2, 6.6 Hz, 3H), 3.71 (t, J = 2.6 Hz, 2H), 3.68–3.59 (m, 1H), 3.57–3.49 (m, 2H), 3.47–3.37 (m, 1H), 2.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.9, 137.8, 129.08, 129.02, 128.6, 128.4, 128.0, 127.9, 127.7, 90.2, 84.6, 77.2, 75.3, 75.0, 74.0, 73.6, 68.3; HRMS calcd for $C_{27}H_{30}N_3O_5$ $[M+H]^+$ 476.2185; found 476.2182.

(2R,3R,4S,5R,6R) -2-azido-4,5-bis(benzyloxy)-6-((benzyloxy) methyl)-3 (methoxymethoxy) tetrahydro-2H-pyran (3): To a solution of secondary hydroxyl compound **2** (1.35 g, 2.83 mmol) dissolved in CH_2Cl_2 (25 mL) was added N,N diisopropylethylamine (DIPEA) (0.74 mL, 4.24 mmol) and MOM-Cl (0.26 mL, 3.39 mmol) at 0 °C followed by addition of a catalytic amount of DMAP. The mixture was stirred at ambient temperature for 24 h and then diluted with CH_2Cl_2 (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography to afford **3** as a yellow oil in 85% (1.25 g) yield; R_f = 0.6 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = -32.2 (c = 0.3, CH_2Cl_2) ; IR (neat) νmax /cm-1: 3258, 2964, 2111, 1059; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 13H), 7.17–7.10 (m, 2H), 4.84 (dd, J = 8.5, 6.0 Hz, 3H), 4.77 (dd, J = 8.5, 4.9 Hz, 2H), 4.62–4.47 (m, 4H), 3.73 (t, J = 3.3 Hz, 2H), 3.66–3.57 (m, 2H), 3.57–3.45 (m, 2H), 3.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.27, 138.25, 138.21, 138.0, 137.99, 137.90, 128.5, 128.0, 127.94, 127.90, 127.87, 127.81, 97.7, 89.8, 84.9, 77.9, 77.4, 77.3, 75.74, 75.72, 75.1, 73.6, 68.4, 56.4; HRMS calcd for $C_{29}H_{37}N_4O_6$ $[M + NH_4]^+$ 537.2713; found 537.2710.

4-nitro-N-((2S,3R,4R,5R)-3,4,6-tris(benzyloxy)-5-hydroxy-2-(methoxy methoxy) hexyl)benzenesulfonamide (4):To a suspension of $LiAlH_4$ (44 mg, 1.15 mmol) in THF (2 mL), was added a solution of compound **3** (300 mg, 0.57 mmol) in THF (3 mL) very slowly at 0 °C. Then the reaction mixture was allowed to warm room temperature and refluxed for 3 h. Upon completion of the reaction (TLC monitoring), it was then cooled to 0 °C and quenched with EtOAc (5 mL) followed by 1N NaOH (5 mL) solution. The resulting white precipitate was removed by filtration through a celite® pad and the filtrate was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (5 mL) followed by brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get the crude amino alcohol. To a stirred solution of the crude amino alcohol (250 mg, 0.50 mmol) in CH_2Cl_2 (7 mL) at 0 °C, was added NEt_3 (105 μL 0.75 mmol), followed by addition of nosyl chloride (166 mg, 0.75 mmol). The reaction mixture was stirred for 2 h at room temperature. Upon consumption of the starting material (TLC monitoring), it was quenched with saturated solution of NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (1 x 5 mL), brine (1 x 5 mL) and dried over Na_2SO_4. Solvent was evaporated and the crude product was purified by column chromatography to give pure compound **4** as a colorless oil in 75% yield (295 mg, over two steps); R_f = 0.3 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = -13.5 (c = 0.2, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3293, 1536, 1361, 678; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 7.34–7.25 (m, 13H), 7.16 (dd, J = 6.5, 2.9 Hz, 2H), 5.61 (s, 1H), 4.63 (dd, J = 9.0, 5.2 Hz, 2H), 4.60–4.55 (m, 2H), 4.54–4.44 (m, 4H), 3.95 (s, 1H), 3.88–3.82 (m, 1H), 3.82–3.76 (m, 1H), 3.73 (dd, J = 7.1, 3.6 Hz, 1H), 3.62 (qd, J = 9.8, 4.4 Hz, 2H), 3.31 (s, 3H), 3.25 (d, J = 13.1 Hz, 1H), 2.94 (dd, J = 13.3, 7.1 Hz, 1H), 2.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 145.8, 137.8, 137.5, 128.59, 128.51, 128.17, 128.13, 127.99, 127.94, 127.8, 127.7, 124.2, 97.8, 78.9, 78.5, 77.4, 74.3, 73.5, 73.2, 71.0, 70.5, 55.9, 44.4; HRMS calcd for $C_{35}H_{41}N_2O_{10}S$ $[M+H]^+$ 681.2482; found 681.2481.

(2S,3R,4R,5S)-3,4-bis (benzyloxy)-2- ((benzyloxy)methyl)-5-(methoxy methoxy)-1-((4-nitrophenyl) sulfonyl)piperidine (5): Triphenylphosphine (578 mg, 2.20 mmol) and diisopropyl azodicarboxylate (432 μL, 2.20 mmol) were added at room temperature to a stirred solution of compound **4** (1 g, 1.47 mmol) in dry toluene (20 mL). The reaction mixture was stirred for a further 5 h and after completion of reaction (TLC monitoring), solvent was evaporated and the crude product was purified by column chromatography to give compound **5** as a yellow oil in 78% (760 mg) yield; R_f = 0.8 (hexane:ethyl acetate = 4:1); $[\alpha]_D^{28}$ = -15.2 (c = 0.1, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3251, 1532, 1091; 1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.9 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H), 7.38–7.24 (m, 13H), 7.13 (dd, J = 6.5, 2.9 Hz, 2H), 4.83–4.62 (m, 7H), 4.50–4.42 (m, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 3.98 (dd, J = 13.4, 5.7 Hz, 1H), 3.71 (d, J = 5.9 Hz, 2H), 3.60 (t, J = 6.7 Hz, 2H), 3.35 (s, 3H), 2.98 (dd, J = 13.5, 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 146.4, 138.6, 137.7, 137.4, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.89, 127.80, 124.0, 97.5, 81.9, 79.2, 75.8, 73.5, 65.5, 55.9, 55.1, 43.8; HRMS calcd for $C_{35}H_{39}N_2O_9S$ $[M + H]^+$ 663.2376; found 663.2372.

(3S,4R,5R,6S)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-((4-nitro phenyl) sulfonyl)piperidin-3-ol (6): To a solution of **5** (600 mg, 0.90 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C, was added trifluroacetic acid (139 μL, 1.81 mmol) and the mixture was stirred for 48 h at room temperature. After completion of the reaction (TLC monitoring), it was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL) and then extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with water (1 x 5 mL), brine (1 x 5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a crude product which was purified by column chromatography to afford pure compound **6** as a colourless liquid in 83% (465 mg) yield; R_f = 0.7 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +1.4 (c = 0.2, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3431, 3036, 1527, 1032; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.9 Hz, 2H), 7.40–7.24 (m, 13H), 7.11 (dd, J = 6.4, 2.8 Hz, 2H), 4.95 (d, J = 11.4 Hz, 1H), 4.69 (s, 2H), 4.62 (d, J = 11.5 Hz, 1H), 4.53 (dd, J = 11.8, 5.8 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H),

4.26 (d, J = 11.5 Hz, 1H), 3.89 (dd, J = 13.5, 5.7 Hz, 1H), 3.73–3.65 (m, 3H), 3.60 (dd, J = 15.1, 10.4 Hz, 1H), 3.51 (t, J = 9.2 Hz, 1H), 2.94 (dd, J = 13.3, 10.9 Hz, 1H), 2.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 146.2, 138.4, 137.5, 137.3, 128.77, 128.74, 128.5, 128.4, 128.2, 128.19, 128.12, 128.0, 127.9, 123.9, 82.6, 79.5, 76.8, 75.4, 73.5, 73.2, 70.1, 65.4, 55.2, 44.3; HRMS calcd for $C_{33}H_{35}N_2O_8S$ $[M+H]^+$ 619.2114; found 619.2113.

(2S,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-1-((4-nitrophenyl) sulfonyl)-1,2,3,4-tetrahydropyridine (7): Compound **6** (100 mg, 0.16 mmol) was dissolved in anhydrous dichloromethane (3 mL) and cooled to 0 °C. Anhydrous pyridine (26 µL, 0.32 mmol) was added to it followed by dropwise addition of trifluoromethanesulfonic anhydride (54 µL, 0.32 mmol). The reaction mixture was stirred at 0 °C for 15 min and after consumption of the starting material (TLC monitoring), it was quenched with water (1 mL). The resulting mixture was then extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was dried with Na_2SO_4, filtered and the solvent removed in vacuo to afford a reddish crude compound. The crude triflate product (110 mg, 0.14 mmol) was dissolved in dry THF (3 mL) and DBU (63 µL, 0.42 mmol) was added to it, and the reaction mixture was refluxed for 1 h. After completion of reaction (TLC monitoring), solvent was evaporated and the crude product purified by column chromatography to give compound **7** as a solid in 71% yield (69 mg, over two steps); m. p = 182-184 °C; R_f = 0.6 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +32.4 (c = 0.3, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3283, 1641, 1532, 816; ^{1}H NMR (500 MHz, CDC_{l3}) δ 8.08 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.36–7.12 (m, 15H), 6.56 (d, J = 8.3 Hz, 1H), 5.05 (dd, J = 8.3, 2.1 Hz, 1H), 4.66–4.57 (m, 4H), 4.43 (d, J = 11.9 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.24 (dd, J = 9.7, 4.8 Hz, 1H), 4.16–4.12 (m, 1H), 3.71 (d, J = 4.7 Hz, 2H), 3.36 (dd, J = 8.3, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 144.6, 138.1, 137.8, 137.6, 128.6, 128.5, 128.4, 128.17, 128.11, 127.9, 127.8, 127.7, 127.4, 124.3, 124.1, 109.2, 75.4, 74.8, 73.3, 72.6, 72.2, 66.7, 56.4; HRMS calcd for $C_{33}H_{36}N_3O_7S$ $[M + NH_4]$+ 618.2274; found 618.2271.

(2S,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5-nitro-1-((4-nitro phenyl)sulfonyl)-1,2,3,4-tetrahydropyridine (8): To a stirred solution of Ac_2O (1 mL) at 10 °C under nitrogen, was added conc. HNO_3 (27 µL, 0.64 mmol) and allowed to stir at -10 °C for 15 min. The reaction mixture was further cooled to -35 °C and compound **7** (110 mg, 0.18 mmol) in Ac_2O (1 mL) was added to the reaction mixture and stirred at same temperature for 45 min. After complete consumption of the starting material (monitored by TLC), the mixture was poured into ice-water (2 mL) and extracted with Et_2O (5 mL x 2). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo to give a crude product. The crude product (106 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled to 0 °C and to it was added NEt_3 (32 µL, 0.22 mmol).[25] After 30 min of stirring at the same temperature, the reaction mixture was quenched with water (2 mL) and extracted with CH2Cl2 (5 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a crude product which was purified by column chromatography to give pure product **8** in 68% (81 mg) yield (over two steps) as a colorless syrup; R_f = 0.5 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +5.6 (c = 0.1, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 2924, 1533, 1178, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.08 (d, J = 9.1 Hz, 2H), 7.76 (d, J = 9.1 Hz, 2H), 7.35–7.24 (m, 15H), 4.80 (d, J = 10.6 Hz, 1H), 4.71 (dd, J = 8.0, 4.9 Hz, 2H), 4.55 (d, J = 11.5 Hz, 1H), 4.44–4.34 (m, 3H), 3.98 (dd, J = 9.6, 4.4 Hz, 1H), 3.86–3.80 (m, 2H), 3.59–3.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 143.2, 137.4, 137.1, 136.8, 135.6, 132.6, 128.7, 128.67, 128.63, 128.5, 128.4, 128.2, 127.8, 124.7, 74.9, 74.6, 73.6, 73.4, 70.7, 66.0, 56.7; HRMS calcd for $C_{34}H_{32}N_3O_{11}S$ $[M + HCO_2]^-$ 690.1758; found 690.1755.

(2S,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-1-(4-methoxy benzyl)-1,2,3,4-tetrahydropyridine (9): To a mixture of **7** (200 mg, 0.33 mmol) in dry CH_3CN (5 mL) at room temperature, K_2CO_3 (137 mg, 0.99 mmol) and thiophenol (40 µL, 0.39 mmol) were added. The reaction mixture was stirred for 10 h at same temperature, and after completion of the reaction (TLC monitoring), the mixture was extracted with ethyl acetate (2 x 5 mL). The organic phase was washed with water (1 x 5 mL) and brine (1 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude amino derivative. The crude amino derivative was subjected to the next reaction without any further purification. Thus, the amino derivative (160 mg, 0.38 mmol) was dissolved in THF (4 mL), to which was added K_2CO_3 (106 mg, 0.77 mmol), NaI (85 mg, 0.57 mmol) and *p*-methoxybenzyl chloride (77 µL, 0.57 mmol) and stirred the same at room temperature for 2 h. Upon consumption of the starting material (TLC monitoring), solvent was concentrated, and then the residue was extracted with EtOAc (2 x 5 mL) and washed with water (2 x 5 mL). Evaporation of the organic solvent gave a crude product which was purified by column chromatography to give compound **9** as a colorless oil in 71% (127 mg) yield; R_f = 0.8 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +46.1 (c = 0.4, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3021, 1618, 1236, 1086; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 17H), 6.87 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 6.3 Hz, 1H), 4.89–4.81 (m, 2H), 4.65 (d, J = 4.5 Hz, 1H), 4.62 (d, J = 4.9 Hz, 1H), 4.55 (d, J = 11.0 Hz, 5H), 4.21 (dd, J = 4.2, 1.5 Hz, 1H), 4.06 (ddd, J = 8.2, 5.0, 2.8 Hz, 1H), 3.86 (dd, J = 8.6, 6.2 Hz, 1H), 3.81–3.76 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 144.8, 138.4, 138.3, 138.1, 130.1, 129.8, 128.53, 128.51, 128.0, 127.9, 127.8, 127.7, 114.2, 100.0, 75.8, 74.5, 73.8, 73.6, 70.6, 68.6, 55.4, 46.4; HRMS calcd for $C_{35}H_{38}NO_4$ $[M + H]^+$ 536.2801; found 536.2800.

(2R,3S,4R,5R,6S)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-(4-methoxybenzyl)-2-vinylpiperidin-3-ol (11): To a stirred solution of **9** (300 mg, 0.56 mmol) in CH_2Cl_2 (4 mL), saturated aqueous $NaHCO_3$ (4 mL) solution and acetone (0.4 mL) were added and cooled to 0 °C. to it was added a solution of Oxone® (689 mg, 1.12 mmol) in H_2O (4 mL) dropwise over 5 min.[26] The reaction mixture was vigorously stirred at the same temperature for 3 h. After completion of the reaction (TLC analysis), the reaction mixture was diluted with 5 mL of CH_2Cl_2 then extracted with CH_2Cl_2 (2 x 5 mL) and washed with water (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give a crude product. The unstable crude product obtained was used without purification. Thus, the crude product (260 mg, 0.47 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C, to which was added vinyl magnesium bromide (315 µL, 2.35 mmol). The reaction mixture was allowed to stir at room temperature for 6 h. After complete consumption of the starting material (TLC analysis), the reaction mixture was cooled to 0 °C and quenched with aqueous NH_4Cl solution (5 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2 x 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to give a crude product which was purified chromatographically to afford pure compound **11** as a syrup in 68% (221 mg) yield; R_f = 0.6 (hexane : ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +28.4 (c = 0.6, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3394, 3019, 1641, 911; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 17H), 6.80 (d, J = 8.6 Hz, 2H), 6.12–6.02 (m, 1H), 5.22 (dd, J = 9.9, 8.3 Hz, 2H), 4.70–4.59 (m, 4H), 4.51 (d, J = 11.7 Hz, 1H), 4.45 (m, 2H), 3.94 (d, J = 2.8 Hz, 1H), 3.90 (dd, J = 8.5, 5.3 Hz, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.80 (s, 3H), 3.78–3.75 (m, 1H), 3.72 (dd, J = 10.7, 3.5 Hz, 1H), 3.66–3.62 (m, 1H), 3.61–3.56 (m, 1H), 3.26 (d, J = 3.6 Hz, 1H), 2.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 138.7, 138.6, 138.5, 132.2, 129.6, 128.5, 128.4, 128.3, 127.8, 127.76, 127.71, 127.63, 127.60, 113.7, 76.5, 73.3, 72.9, 72.52, 63.6, 55.3, 53.3; HRMS calcd for $C_{37}H_{42}NO_5$ $[M + H]^+$ 580.3063; found 580.3061.

(2R,3S,4R,5R,6S)-2-ethyl-6-(hydroxymethyl) piperidine-3,4,5-triol (12): Compound **11** (100 mg, 0.17 mmol) was dissolved in CH_3OH (3 mL) and $Pd(OH)_2/C$ (20% w/w, 20 mg) was added to it. The solution was degassed and then stirred under 1 atm of H_2 (balloon) for 24 h. The catalyst was filtered through a Celite® pad and the filtrate concentrated in vacuo. The residue was purified by repeated washing with 50% CH_2Cl_2–hexane to get pure product **12** as a syrup in 68% (22 mg) yield. ^{1}H NMR (400 MHz, D_2O) δ 4.12 (t, J = 2.9 Hz, 1H), 4.02 (m, 2H), 3.92–3.79 (m, 2H), 3.62–3.51 (m, 1H), 3.39 (dd, J = 9.8, 4.5 Hz, 1H), 1.88–1.69 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 66.95, 66.92, 66.4, 59.1, 56.86, 56.84, 20.8, 8.6; HRMS calcd for $C_8H_{18}NO_4$ $[M + H]^+$ 192.1236; found 192.1234.

(2R,3R,4R,5R,6S)-3-azido-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-(4-methoxybenzyl)-2-vinylpiperidine (13):To a well stirred solution of 11 (200 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was added mesyl chloride (40 μL, 0.51 mmol) and Et_3N (71 μL, 0.51 mmol) and the reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (TLC monitoring), aqueous $NaHCO_3$ solution (5 mL) was added to it. Extraction was done with CH_2Cl_2 (3 x 5 mL), and the solvent evaporated in vacuo to give crude mesylate. The crude mesylate product was subjected to the next step without purification. Thus, the crude mesylate (220 mg, 0.33 mmol) was dissolved in DMF (5 mL) and to this NaN_3 (44 mg, 0.67 mmol) was added, and the reaction mixture stirred at 65 °C for 18h. On complete consumption of the starting material (TLC monitoring), ice cold water (10 mL) was added to it. The desired compound was extracted with EtOAc (2 x 10 mL), and the extracts were dried over Na_2SO_4. The solvent was evaporated using a rotary evaporator and the residue purified by column chromatography to obtain 134 mg (64% yield over 2 steps) of compound **13** as a colorless syrup. R_f = 0.8 (hexane:ethyl acetate = 4:1); $[\alpha]_D^{28}$ = +16.0 (c = 0.2, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 2932, 2116, 1610, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 17H), 6.85 (d, J = 8.6 Hz, 2H), 6.07–6.01 (m, 2H), 5.59 (d, J = 17.0 Hz, 1H), 5.10 (d, J = 10.8 Hz, 1H), 4.87 (m, 2H), 4.65 (m, 4H), 4.47 (m, 3H), 4.24 (m, 2H), 3.97 (m, 3H), 3.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 150.8, 138.54, 138.52, 138.2, 131.5, 130.1, 129.7, 128.4, 128.3, 128.2, 127.8, 127.71, 127.70, 127.6, 127.5, 127.3, 126.1, 120.3, 120.2, 115.1, 114.1, 101.2, 75.9, 73.4, 73.3, 71.8, 71.0, 70.9, 68.3, 55.3, 46.3; HRMS calcd for $C_{37}H_{44}N_5O_4$ $[M + NH_4]^+$ 622.3393; found 622.3391.

N-((2R,3R,4R,5R,6S)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-(4-methoxybenzyl)-2-vinylpiperidin-3-yl)acetamide (14): To a stirred solution of **13** (100 mg, 0.165 mmol) in acetic anhydride (2 mL) at 0 °C, was added Zn dust (356 mg, 5.44 mmol) and acetic acid (849 μL, 14.85 mmol).[28] The reaction mixture was allowed to stir for 3 h at room temperature. It was then filtered through Celite® and filtrate extracted with EtOAc (2 X 5 mL) and washed with water (2 X 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography to get pure compound **14** as a colorless oil in 78% (80 mg) yield; R_f = 0.4 (hexane:ethyl acetate = 4:2); $[\alpha]_D^{28}$ = +48.6 (c = 0.6, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3352, 2891, 1671, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 17H), 7.15 (bs, 1H), 6.88 (dd, J = 6.6, 4.9 Hz, 2H), 6.03–5.92 (m, 2H), 5.41–5.39 (m, 1H), 5.09–5.06 (m, 1H), 4.77 (dd, J = 10.2, 2.9 Hz, 4H), 4.67–4.61 (m, 3H), 4.54–4.49 (m, 4H), 3.83–3.80 (m, 3H), 3.72–3.69 (m, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 159.7, 138.5, 138.1, 138.0, 131.3, 130.1, 129.7, 128.5, 128.4, 128.1, 127.97, 127.90, 127.8, 127.79, 127.73, 120.6, 114.2, 80.6, 78.1, 75.2, 75.1, 75.0, 73.6, 73.3, 73.1, 72.5, 68.9, 55.4, 46.3, 21.0; HRMS calcd for $C_{39}H_{45}N_2O_5$ $[M+H]^+$ 621.3328; found 621.3325.

N-((2S,3R,4R,5R,6S)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-(hydroxymethyl)-1-(4-methoxybenzyl)piperidin-3-yl)acetamide (15): To a stirred solution of **14** (70 mg, 0.11 mmol) in a mixture of tBuOH, acetone, and H_2O (1:5:1; 4 mL), was added N-methylmorpholine N-oxide (20 mg, 0.17 mmol) and OsO_4 (0.01 mmol). The reaction mixture was allowed to stir for 24 h at room temperature. It was then quenched with saturated aqueous $Na_2S_2O_5$ solution (5 mL), and allowed to stir for 1 h at room temperature. Then the mixture was extracted with EtOAc (3 × 5 mL), and the combined extracts were dried over Na_2SO_4, and concentrated to give a crude diol product. The crude diol (61 mg, 0.09 mmol) was dissolved in THF:H_2O (2:1; 2 mL), cooled to 0 °C and to it was added $NaIO_4$ (40 mg, 0.186 mmol) and allowed the mixture to stir at room temperature for 5 h. Upon completion of staring material (monitored by TLC), the reaction mixture was filtered, and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phase was washed with brine (1 x 5 mL), and the solvent evaporated to give the crude product aldehyde, which was used for the next step without purification. Thus, to a cooled solution of crude aldehyde (56 mg, 0.08 mmol) in MeOH (2 mL) at 0 °C was added $NaBH_4$ (7 mg, 0.18 mmol), and the reaction mixture stirred at the same temperature for 2 h. Upon consumption of the starting material (TLC monitoring), it was quenched with saturated aqueous NH_4Cl solution (3 mL). Methanol was evaporated and extraction was done with CH_2Cl_2 (2 x 5 mL) and washed with water (2 x 5mL). The combined organic extracts were dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue afforded **15** in 71% (50 mg) yield (over three steps) as a colorless syrup; R_f = 0.4 (hexane:ethyl acetate = 1:1); $[\alpha]_D^{28}$ = +62.7 (c = 0.4, CH_2Cl_2); IR (neat) νmax /cm^{-1}: 3542, 1668, 1272; 1034; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 17H), 6.87 (d, J = 8.7 Hz, 2H), 4.56 (m, 5H), 4.53–4.50 (m, 1H), 4.49 (d, J = 3.6 Hz, 2H), 4.39 (d, J = 9.1 Hz, 1H), 4.16 (dd, J = 12.0, 5.5 Hz, 2H), 3.96 (br s, 1H), 3.84–3.77 (m, 7H), 3.69 (dd, J = 10.1, 6.2 Hz, 1H), 3.64 (dd, J = 6.7, 3.6 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 159.8, 138.1, 137.7, 137.1, 130.1, 129.8, 128.6, 128.5, 128.2, 128.1, 128.0, 127.85, 127.80, 127.7, 127.6, 114.2, 75.4, 74.5, 73.7, 73.4, 72.8, 72.4, 69.4, 68.8, 67.7, 67.0, 66.5, 55.4, 46.4, 21.0; HRMS calcd for $C_{38}H_{45}N_2O_6$ $[M + H]^+$ 625.3278; found 625.3274.

N-((2S,3R,4R,5R,6S)-4,5-dihydroxy-2,6-bis(hydroxymethyl)piperidin-3-yl)acetamide (16): Compound **15** (50 mg, 0.08 mmol) was dissolved in CH_3OH (2 mL), and $Pd(OH)_2/C$ (10 mg, 20% w/w) was added to it. The reaction mixture was allowed to stir under 1 atm of H_2 (balloon) at room temperature for 20 h. When the reaction was complete, the mixture was filtered through a pad of Celite® and washed with MeOH. The filtrate was concentrated and the residue washed repeatedly with hexane to give pure product **16** as white syrup in 62% (19 mg) yield; $[\alpha]_D^{28}$ = +12.7 (c = 0.1, D_2O); IR (neat) νmax /cm^{-1}: 3415, 2924, 1672, 1038; ^{1}H NMR (500 MHz, D_2O) δ 4.41 (ddd, J = 8.7, 5.7, 2.5 Hz, 1H), 4.36–4.33 (m, 1H), 4.23 (dd, J = 10.4, 4.8 Hz, 1H), 3.98 (dd, J = 5.3, 3.6 Hz, 1H), 3.87–3.81 (m, 2H), 3.74 (t, J = 6.1 Hz, 1H), 3.65–3.62 (m, 1H), 3.47 (t, J = 8.0 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 174.3, 76.4, 73.3, 71.7, 71.0, 69.3, 67.2, 65.8, 60.6, 20.3; HRMS calcd for $C_9H_{19}N_2O_5$ $[M + H]^+$ 235.1294; found 235.1291.

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[1] a) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem*. **1996**, *108*, 1482–1522; *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419; b) P. H. Seeberger, W.-C. Haase, *Chem. Rev.* **2000**, *100*, 4349–4393; c) P. Pal, A. K. Shaw, *RSC Adv*. **2017**, *7*, 25897–25963.

[2] a) R. J. Ferrier, *Topics in Current Chemistry* **2001**, *215*, pp 153–175, ed. A. E. Stutz; b) P. Collins, R. Ferrier, *Monosaccharides: Their chemistry and Their Roles in Natural Products*, Wiley, Chichester, **1995**; c) A. A. Ansari, R. Lahiri, Y. D. Vankar, *ARKIVOC* **2013**, *(ii)*, 316–362; d) A. L. de Moura, L. M. A. de Lima, G. B. Bezerra, J. J. R. de Freitas, M. F. Belian, C. S. Ramos, R. A. Avelino, J. R. de Freitas Filho, *Quim. Nova*. **2018**, *41*, 550–566.

[3] a) R. R. Schmidt, Y. D. Vankar, *Acc. Chem. Res*. 2008, *41*, 1059–1073; b) T. Delaunay, T. Poisson, P. Jubault, X. Pannecoucke, *Eur. J. Org. Chem.* **2014**, 7525–7546.

[4] a) M. Leibeling, D. C. Koester, M. Pawliczek, D. Kratzert, B. Dittrich, D. B. Werz, *Bioorg. Med. Chem*. **2010**, *18*, 3656–3667; b) S. Dharuman, Y. D. Vankar, *Org. Lett*. **2014**, *16*, 1172–1175.

[5] N. G. Ramesh, *Eur. J. Org. Chem*. **2014**, 689–707 and references cited therein.

[6] a) T. Sakakibara, T. Suganuma, Y. Kajihara, *Chem. Commun*. **2007**, 3568–3570; b) T. Pathak, *Tetrahedron* **2008**, *64*, 3605–3628.

[7] F. W. Lichtenthaler, *Chem. Rev*. **2011**, *111*, 5569–5609.

[8] a) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624–1672; *Angew. Chem. Int. Ed*. **2001**, *40*, 1576–1624; b) R. Lahiri, S. Dharuman, Y. D. Vankar, *Chimia*, **2012**, *66*, 905–912.

[9] a) N. Asano, *Glycobiology* **2003**, *13*, 93R–104R; b) V. H. Lillelund, H. H. Jensen, X. Liang M. Bols, *Chem. Rev*. **2002**, *102*, 515–553; c) K. Afarinkia, A. Bahar, *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1287.

[10] a) Y. Ichikawa, Y. Igarashi, M. Ichikawa, Y. Suhara, *J. Am. Chem. Soc*. **1998**, *120*, 3007–3018; b) E. Truscheit, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, W. Wingender, *Angew. Chem*. **1981**, *93*, 738–755; *Angew. Chem. Int. Ed*. **1981**, *20*, 744–761.

[11] N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.

[12] a) J. Alper, *Science* **2001**, *291*, 2338–2343; b) G. W. J. Fleet, D. R. Witty, *Tetrahedron: Asymmetry* **1990**, *1*, 119–136.

[13] A. E. Stutz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH: Weinheim, **1999**.

[14] a) F. Gomollón-Bel, I. Delso, T. Tejero, P. Merino, *Curr Chem Biol*. **2014**, *8*, 10–16; b) T. Kajimoto, K. K.-C. Liu, R. R. Pederson, Z. Zhong, Y. Ichikawa, J. A. Jr. Porco, C-H. Wong, *J. Am. Chem. Soc*. **1991**, *113*, 6187–6196.

[15] a) R. A. Dwek, T. D. Butters, F. M. Platt, N. Zitzman, *Nat. Rev. Drug Discovery*. **2002**, *1*, 65–75; b) A. Mitrakou, N. Tountis, A. E. Raptis, R. J. Bauer, H. Schulz, S. A. Raftis, *Diabetes. Med*. **1998**, *15*, 657–660.

[16] O. Abian, P. Alfonso, A. Velaz-quez-Campoy, P. Giraldo, M. Pocovi, J. Sancho, *Mol. Pharm*. **2011**, *8*, 2390–2397.

[17] K. Ikeda, M. Takahashi, M. Nishida, M. Miyauchi, H. Kizu, Y. Kameda, M. Arisawa, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano, *Carbohydr. Res*. **2000**, *323*, 73–80.

[18] a) M. S. M. Pearson, M. Evain, M. Mathé-Allainmat, J. Lebreton, *Eur. J. Org. Chem*. **2007**, 4888–4894; b) M. A. T. Maughan, I. G. Davies, T. D. W. Claridge, S. Courtney, P. Hay, B. G. Davis, *Angew. Chem*. **2003**, *115*, 3918–3922; *Angew. Chem., Int. Ed*. **2003**, *42*, 3788–3792; c) M. Mondon, F. Lecornué, J. Guillard, S. Nakagawa, A. Kato, Y. Blériot, *Bioorg. Med. Chem*. **2013**, *21*, 4803–4812; d) M. S. N. Pearson, R. O. Saad, T. Dintinger, H. Amri, M. Mathé-Allainmat, J. Lebreton, *Bioorg. Med. Chem*. **2006**, *16*, 3262–3267.

[19] a) J. Désiré, P. J. Dransfield, P. M. Gore, M. Shipman, *Synlett* **2001**, *8*, 1329–1331; b) J. Désiré, M. Shipman, *Synlett*, **2001**, *8*, 1332–1334; c) P. J. Dransfield, P. M. Gore, M. Shipman, A. M. Z. Slawin, *Chem. Commun*. **2002**, 150–151; d) P. J. Dransfield, P. M. Gore, I. Prokes, M. Shipman, A. M. Z. Slawin, *Org. Biomol. Chem*. **2003**, *1*, 2723–2733.

[20] a) D. L. Comins, A. B. Fulp, *Tetrahedron Lett*. **2001**, *42*, 6839–6841; b) D. L. Comins, M. J. Sandelier, T. A. Grillo, *J. Org. Chem*. **2001**, *66*, 6829–6832.

[21] a) N. Kumari, Y. D. Vankar, *Org. Biomol. Chem*. **2009**, *7*, 2104–2109; b) A. Kumar, G. K. Rawal, Y. D. Vankar, *Tetrahedron*, **2008**, *64*, 2379–2390; c) B. G. Reddy, Y. D Vankar, *Angew. Chem.* **2005**, *117*, 2037–2040; *Angew. Chem., Int. Ed*. **2005**, *44*, 2001–2004; d) P. Gupta, A. P. J. Pal, Y. S. Reddy, Y. D. Vankar, *Eur. J. Org. Chem*. **2011**, 1166–1175; e) A. P. J. Pal, P. Kadigachalam, A. Mallick, D. V. Ramana, Y. D. Vankar, *Org. Biomol. Chem*. **2011**, *9*, 809–819; f) P. Gupta, S. Dharuman, Y. D. Vankar, *Tetrahedron: Asymmetry* **2010**, *21*, 2966–2972; f) A. Mallick, N. Kumari, R. Roy, A. Palanivel, Y. D. Vankar, *Eur. J. Org. Chem*. **2014**, 5557–5563; g) A. A. Ansari, P. Rajasekaran, M. M. Khan, Y. D. Vankar, *J. Org. Chem.* **2014**, *79*, 1690–1699; h) R. Lahiri, A. Palanivel, S. A. Kulkarni, Y. D. Vankar, *J. Org. Chem*., **2014**, *79*, 10786–10800.

[22] Y. S. Reddy, A. P. J. Pal, P. Gupta, A. A. Ansari, Y. D. Vankar, *J. Org. Chem*. **2011**, *76*, 5972–5984.

[23] Please see the Electronic Supporting Information (ESI) for spectral details.

[24] a) P. K. Kancharla, Y. D. Vankar, *J. Org. Chem*. **2010**, *75*, 8457–8464; b) P. K. Kancharla, Y. S. Reddy, S. Dharuman, Y. D. Vankar, *J. Org. Chem*. **2011**, *76*, 5832–5837; c) S. Dharuman, P. Gupta, P. K. Kancharla, Y. D. Vankar, *J. Org. Chem*. **2013**, *78*, 8442–8450.

[25] J. Das, R. R. Schmidt, *Eur. J. Org. Chem*. **1998**, 1609–1613.

[26] P. Cheshev, A. Marra, A. Dondoni, *Carbohydr. Res*. **2006**, *341*, 2714–2716.

[27] Y. Blériot, N. Auberger, Y. Jagadeesh, C. Gauthier, G. Prencipe, A. Yamamoto, A. Kato, M. Sollogoub, *Org. Lett*. **2014**, *16*, 5512–5515.

[28] R. J. Payne, S. Ficht, S. Tang, A. Brik, Y. Y. Yang, D. A. Case, C. H. Wong, *J. Am. Chem. Soc*. **2007**, *129*, 13527–13536.

[29] Y.-T. Li, S.-C. Li, *Methods in Enzymology*, ed. V. Ginsberg, Academic Press, New York, **1972**, vol. *28*, Part B, p. 702.

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FULL PAPER

A simple and efficient stereoselective synthesis of an imino glycal is demonstrated in 8 steps starting from 1,2-anhydro-3,4,6-tri-O-benzyl-D-glucopyranose. The utility of the imino glycal has been shown in synthesis of (–)-1-*epi*-adenophorine and a homoiminosugar as a glycosidase inhibitor.

From Glycal to Imino glycal

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A Stereoselective Synthesis of an Imino Glycal: Application in the Synthesis of (–)-1-*epi*-Adenophorine and a Homoiminosugar