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PAPER

Aza-Claisen rearrangement of 2-*C*-hydroxymethyl glycals as a versatile strategy towards synthesis of isofagomine and related biologically important azasugars†

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Synthesis of isofagomine has been achieved by implementation of aza-Claisen rearrangement of 2-*C*-hydroxymethyl glycals as a key step. The above rearrangement has also been utilized in the synthesis of biologically important polyhydroxylated piperidine frameworks such as isogalactofagomine, ent-isogalactofagomine and their analogues and some other azasugars as glycosidase inhibitors.

Introduction

Since the discovery of 1-deoxynojirimycin[1] **1** (DNJ), design and synthesis of polyhydroxylated piperidines, also called aza sugars or iminosugars, have gained huge importance in recent times.[2,3] These molecules have been targets for possible therapeutic uses ranging from diabetes,[4] cancer,[5] HIV[6] and other metabolic disorders.[7] Among them Miglitol **2** (*N*-hydroxylethyl-1-deoxynojirimycin) and Zavesca **3** (*N*-butyl-1-deoxynojirimycin) are being used as drugs in the treatment of type II diabetes and type I Gaucher's disease respectively (Fig. 1). Isofagomine **4A** is also another important polyhydroxylated piperidine analogue, designed by Bols *et al.*[8] and is a selective and strong inhibitor of β-glucosidase [K_i = 0.11 μM, sweet almonds].[8,9] The rationale behind the design of isofagomine is the fact that it could act as an apparent transition state analogue that mimics the oxycarbenium ion-like transition state in which the positive charge resides at the anomeric carbon.[9] The tartrate salt of isofagomine is a designed drug for the treatment of Gaucher's disease,[10,11] which apparently[12] failed in phase III clinical trials. It is an active-site inhibitor, and it increases GlcCerase activity by 3.0 ± 0.6 fold in N370S fibroblasts by several mechanisms.[13] Furthermore, isogalactofagomine **5**, a stereoisomer of isofagomine, has been reported to be a selective and potent inhibitor of β-galactosidases [K_i = 0.004 μM, *Aspergillus oryzae*].[14] Likewise, the L-fucosidase inhibitor **6** was synthesized by Bols *et al.*[15] and found to be active in micromolar range (K_i = 6.4 μM, *Human placenta*). Ichikawa *et al*[16] have reported the synthesis of galactose-type azasugar **8** (Fig. 2), with an extra hydroxyl group at C-3, which is a specific and potent inhibitor against β-galactosidase (K_i = 5.7 μM). Owing to the above mentioned importance and selective inhibition activities there has been an increased interest towards the development of general and flexible methodologies for the synthesis of such polyhydroxylated frameworks through a common precursor.[17]

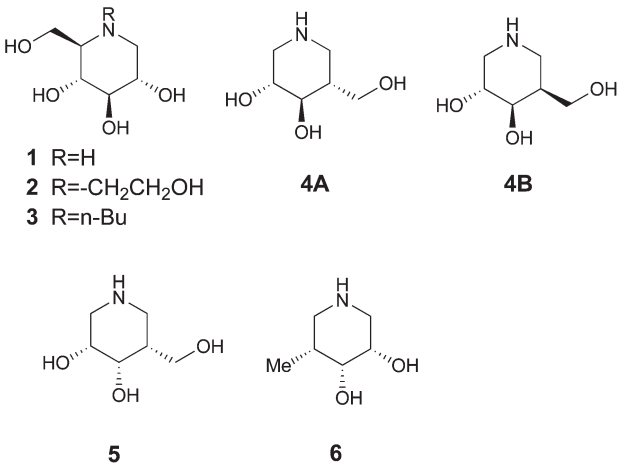

Fig. 1 Piperidine based imino- and azasugars.

Aza-Claisen rearrangement (or Overman rearrangement) constitutes a mild and powerful tool for the synthesis of several nitrogen containing natural products in organic as well as in medicinal chemistry.[18] In this rearrangement the reaction of an allylic alcohol with trichloroacetonitrile is carried out either under thermal conditions or by Hg(II) or Pd(II) catalysis to form allylic trichloroacetamide *via* the rearrangement of the corresponding trichloroacetimidate.[17d] This rearrangement has also been explored in the area of carbohydrate chemistry.[18d,19,20] Thus, Nguyen *et al.*[19] have utilized palladium-catalyzed aza-

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†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds, and 2D-COSY, NOE, DEPT-135 spectras of some selected compounds. See DOI: 10.1039/c2ob06851f

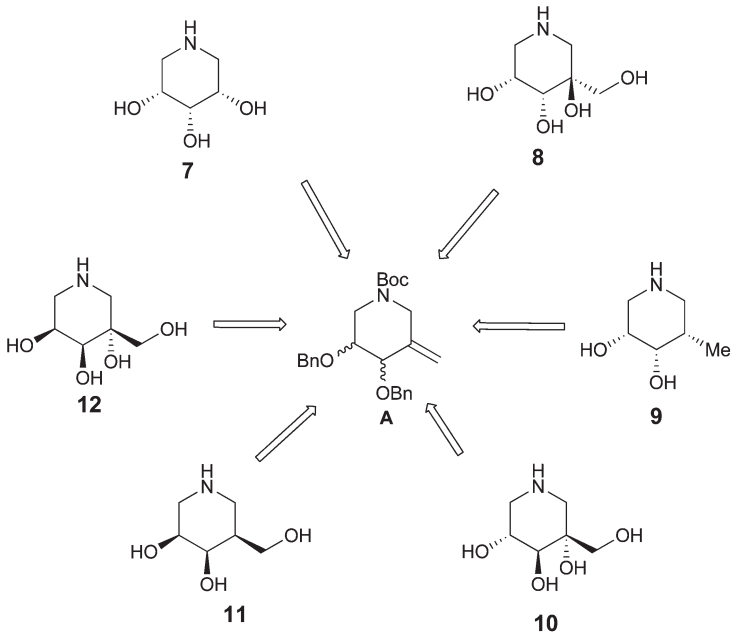
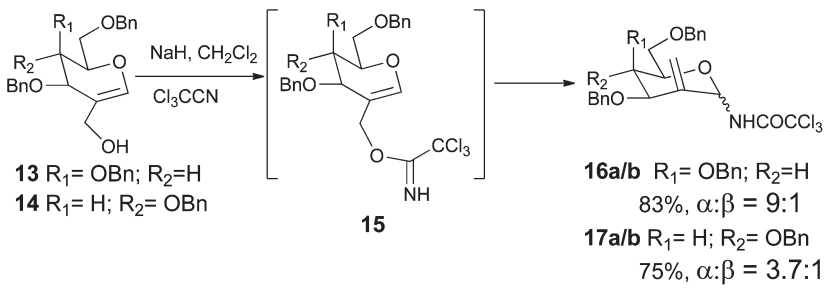


Fig. 2 Strategy for the construction of biologically important azasugars.

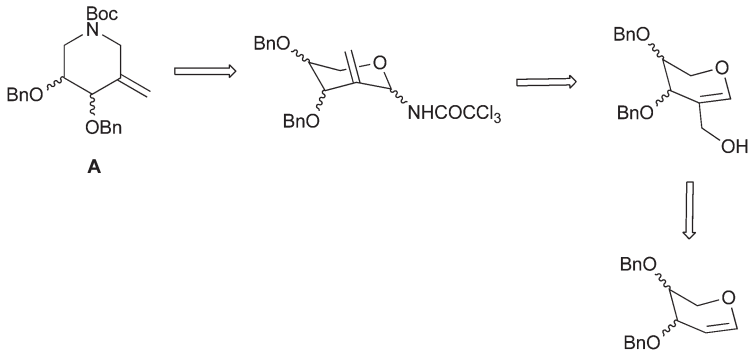


Scheme 1 One-pot rearrangement of 2-hydroxyglycals.

Claisen rearrangement of glycals as a key step for the synthesis of glycosyl urea derivatives. In these reactions, the C-3 free hydroxyl group was reacted with trichloroacetonitrile under palladium catalysis to afford stereoselectively the 2,3-unsaturated α- and β-*N*-glycosyl amides by introducing the nitrogen atom at the anomeric center. It is well known that the presence of a nitrogen atom at the anomeric carbon permits easy access towards the synthesis of monocyclic[21a,b,c] and bicyclic iminosugars.[21d,e] More recently, we reported[21a] the aza-claisen rearrangement of gluco and galacto derived C-2 hydroxymethyl glycals (*vide infra*) *en route* to some iminosugars. Thus, when 3,4,6-tri-*O*-benzyl-2-*C*-hydroxymethyl galactal **13** (Scheme 1) was treated with trichloroacetonitrile and NaH at room temperature, we observed the formation of the rearranged trichloroacetamide **16** instead of the expected trichloroacetimidate **15**. Clearly, the imidate formation and subsequent rearrangement seem to occur in the same pot without any catalysis or need of high temperature. We have shown the utility of these rearranged products in the synthesis of L-allo-deoxynojirimycin and two new azasugars, *viz.* 5-(hydroxymethyl) analogues of L-altro- and L-ido-deoxynojirimycin[21a] and these were found to be moderate glycosidase inhibitors. Our continued interest in developing newer approaches towards the synthesis of glycosidase inhibitors,[22,23] and the importance of isofagomine and its analogs (*vide supra*) led us to explore the potential of the aza-Claisen rearrangement of 2-*C*-hydroxymethyl glycals derived from D-arabinal, L-arabinal and D-xylal to synthesise isofagomine and related azasugars. The retrosynthetic analysis for our approach is shown in Scheme 2.

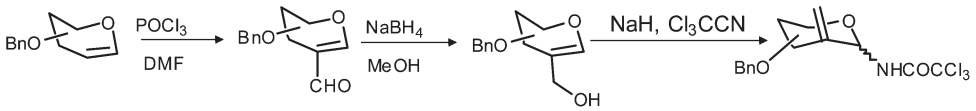
Results and discussion

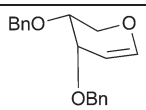
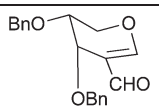
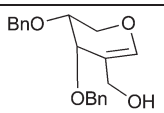
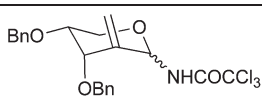
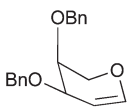
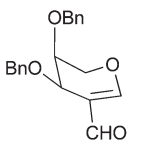
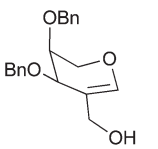
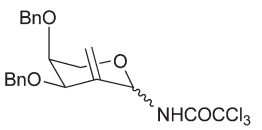
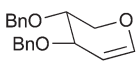
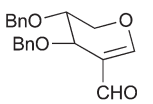
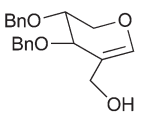
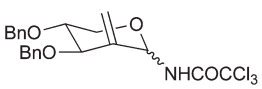
Thus, our synthesis emanated from 3,4-di-*O*-benzyl-D-arabinal **18** (Table 1), derived from D-arabinose, which upon Vilsmeier–Haack formylation using phosphoryl chloride and *N,N*-dimethylformamide yielded the corresponding 2-formyl pentose glycal **19** in good yield which was characterised by its spectral data. Thus, in its ^{1}H NMR spectrum a sharp singlet around δ 9.35, and in the ^{13}C NMR spectrum a peak at δ 189 were observed. Furthermore, in the IR spectrum a sharp band at 1621 cm^{-1} for the conjugated formyl group was visible which asserted the formation of the desired product. Reduction of aldehyde **19** with sodium borohydride in methanol furnished the 2-*C*-hydroxymethyl 3,4-di-*O*-benzyl-D-arabinal **20** in 85% yield. The



Scheme 2 Retrosynthetic analysis for the synthesis of common intermediate **A**.

Table 1 Conversion of 2-*C*-hydroxymethyl glycals into rearranged products

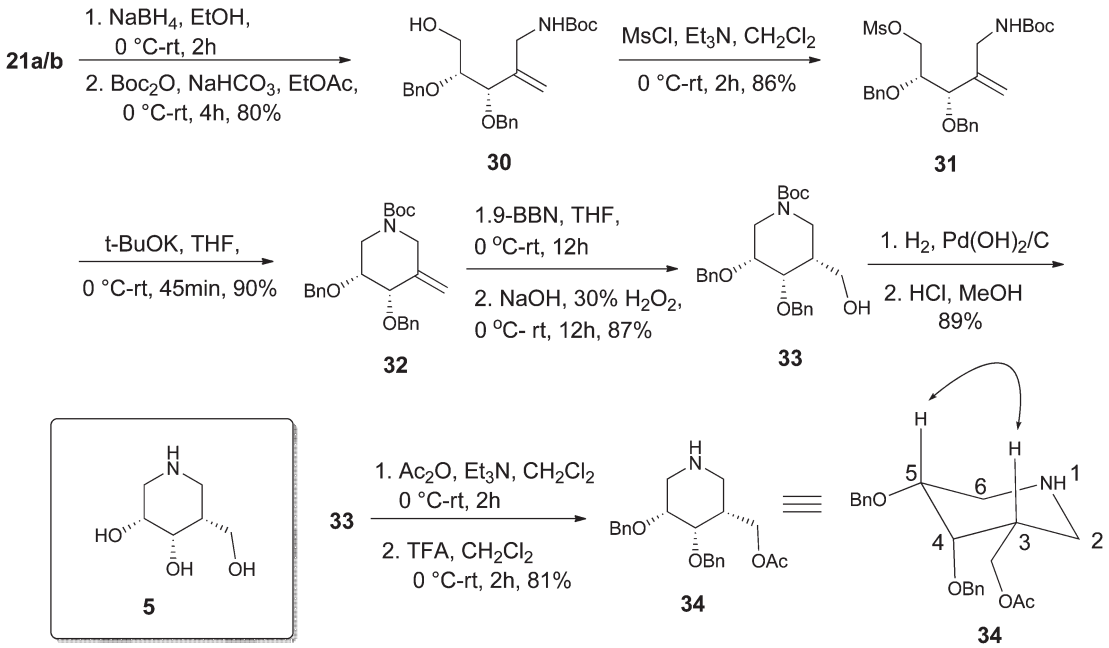


Entry	Glycal	Aldehyde	C-2 hydroxy glycal	1-Azido sugar
1	 **18**	 **19** (73%)	 **20** (85%)	 **21a/b** (88%) α:β = 8.5:1.5
2	 **22**	 **23** (73%)	 **24** (85%)	 **25a/b** (88%) α:β = 8.5:1.5
3	 **26**	 **27** (44%)	 **28** (80%)	 **29a/b** (78%) α:β = 1:1

disappearance of the corresponding –CHO group signals in the ^{1}H and ^{13}C NMR spectra of compound **20** confirmed the formation of the reduced product which was subjected to the aza-Claisen rearrangement. Thus, treatment of 2-*C*-hydroxymethyl 3,4-di-*O*-benzyl-D-arabinal **20** with trichloroacetonitrile and NaH in dichloromethane at room temperature provided an inseparable mixture of α/β-*N*-glycosyl trichloroacetamidate **21a/b** in 8.5 : 1.5 ratio and in 88% yield, as confirmed from the spectral data (see Experimental section and ESI†).

Likewise, 3,4-di-*O*-benzyl-L-arabinal **22** and 3,4-di-*O*-benzyl-D-xylal **26** were subjected to formylation[24] followed by reduction and treatment with trichloroacetonitrle to lead to rearrangement furnishing the trichloroacetamides **25** and **29** respectively in good yields.

With these rearranged products (glycosyl amides) in hand, we turned our attention towards the conversion of these products into polyhydroxylated sugar intermediates. For this purpose, reduction of amide accompanied by ring opening was executed. Thus, reaction of amide **21a/b** with $NaBH_4$ in EtOH resulted in the formation of the corresponding free amine which was immediately treated with di-*tert*-butyl dicarbonate to obtain Boc-protected amine **30** (Scheme 3) in 80% yield. Mesylation of the amino alcohol **30** proceeded smoothly affording **31** in good yield. In our earlier report,[21a] we employed intramolecular S_N2 cyclization that was triggered by the deprotection of –NHBoc group using CF_3COOH in CH_2Cl_2 followed by treatment with K_2CO_3. But in the present study, to reduce the number of steps and to retain the –NHBoc group for synthetic manipulations, we



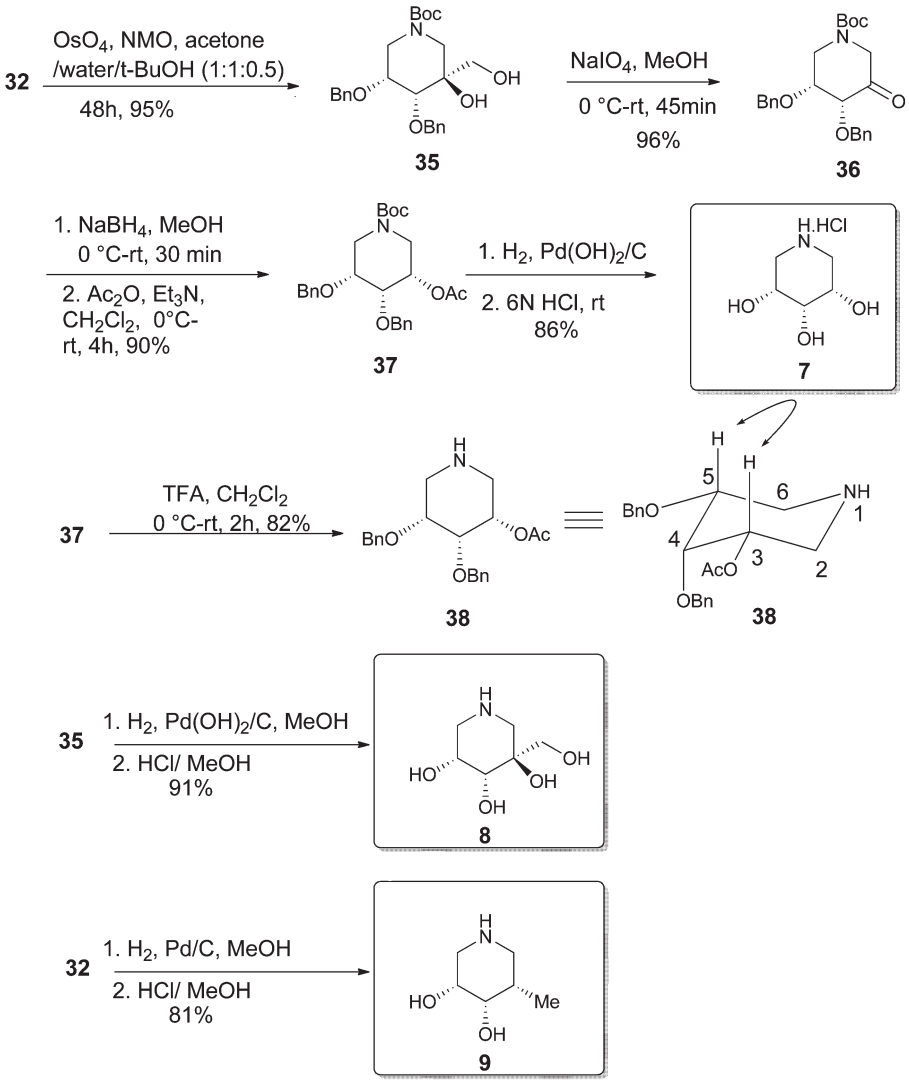
Scheme 3 Synthesis of azasugar **5**.

have carried out one pot, intramolecular S_N2 cyclization with *t*-BuOK to obtain the cyclized product **32** in 90% yield. The structure of the product was confirmed by spectral analysis. In its ^{1}H-NMR spectrum the absence of –OMs peak at δ 2.91 and appearance of $[M + Na]^+$ peak at 432.2154 (calculated 432.2145) in its high resolution mass spectrum confirmed that cyclization had occurred. It is expected that synthon **32** could be easily converted into various targets by suitably functionalizing the exocyclic double bond. In the present study, compound **32** was subjected to hydroboration–oxidation with 9-BBN/H_2O_2 to lead to the monohydroxy compound **33** in 87% yield as a single diastereomer. However, because of the presence of rotamers, the determination of exact stereochemistry was difficult at this stage. Thus, acetylation of **33** followed by removal of the NHBoc protection gave compound **34** whose spectral data, including COSY and NOE experiments, permitted the assignment of the stereochemistry at the newly generated stereocenter. Thus, in an NOE experiment, irradiation of signal for H-5 at δ 3.54 enhanced the signal H-3 at δ 1.99 and there was no enhancement of H-7and H-7′ at δ 4.10. This confirmed the absolute configuration at the newly generated stereocenter to be '*R*'. The reason for the selectivity may be attributed to the selective hydroboration of **32** from the β-face, possibly due to the preferential low energy equatorial orientation of the bulky bicyclic boron in the four membered transition state. Finally, deprotection of compound **33** was carried out in two steps *viz.* hydrogenolysis of benzyl groups using catalytic $Pd(OH)_2/C–H_2$ and deprotection of NHBoc employing acidic conditions that gave the deprotected compound **5** in 89% yield. Spectral data for **5** were in complete agreement with those reported in literature.[14]

Kusano and co-workers isolated the piperidine triol[25] **7** and its analogues from the *Eupatoriumfortunei* TURZ and found them to be active components of the extracts of this plant.[25] These are traditionally used in Japanese and Chinese and folk medicines as diuretic, antidiabetic, emmenagogue, and antipyretic agents.[25] These have also been found to be moderate glycosidase inhibitors.[26] We realized that olefin **32** could be an ideal precursor for the synthesis of this molecule. Thus, compound **32** was subjected to dihydroxylation using a catalytic amount of osmium tetroxide and NMO to afford a diol **35** as a single diastereomer (Scheme 4). It was oxidatively cleaved with sodium periodate affording the corresponding ketone **36** whose reduction with sodium borohydride followed by acetylation of the crude product gave **37** as a single diastereomer. Deprotection of N-Boc was carried out by using TFA in methylene chloride affording the free amine in quantitative yield. The stereochemistry of the newly generated hydroxyl group was confirmed by the COSY and NOE experiments of **38** (Scheme 4). Thus, irradiation of the signal for H-3 led to the enhancement of the signal for H-5 proton confirming the absolute configuration at the newly generated center to be *S*. These correlations revealed that the reduction had only occurred from the less hindered side of the carbonyl moiety. Finally, compound **37** was subjected to hydrogenolysis under catalytic $Pd(OH)_2/C–H_2$ conditions, followed by treatment with aq. 6 N HCl for the removal of acetate and –NHBoc protections to provide triol **7** which was characterized as its hydrochloride salt. Its spectral data were in complete agreement with those reported in literature.[26c,d]

Compound **8** is a selective potent inhibitor (*vide supra*) and in the present study we have achieved its synthesis from diol **35**. Thus, diol **35** was subjected to hydrogenolysis followed by acid treatment to provide the polyhydroxylated azasugar **8** (Scheme 4) in 91% yield. The spectral data is in absolute match with the literature data[16] for it. Likewise, when compound **32** was subjected to hydrogenolysis and acid treatment it provided the azasugar **9**, which is a mirror image of the fucosidase inhibitor **6**, in 81% yield and the data was in complete agreement with the previously reported data (Scheme 4).[27]

Likewise, glycosyl amides **29a/b** were transformed into isofagomine **4A** and 5-*epi*-isofagomine **4B** (Scheme 5). The reaction



Scheme 4 Synthesis of azasugars **7**, **8**, **9**.

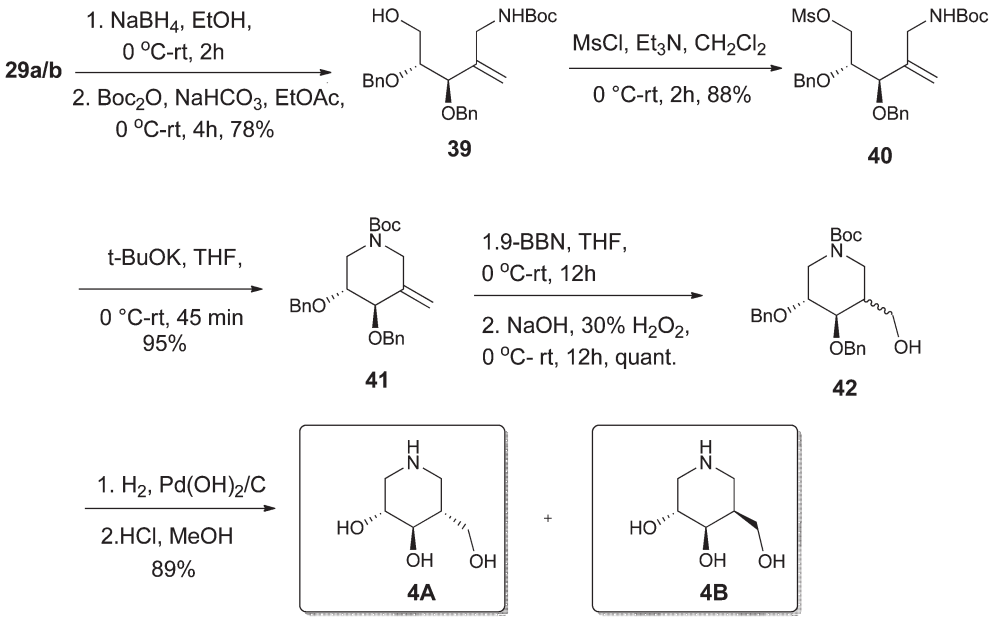
of an anomeric mixture of **29a/b** with $NaBH_4$ in ethanol afforded the ring opened free amine, –NHBoc protection of which furnished **39** in 78% yield. Mesylation of this amino alcohol followed by cyclization provided the expected product **41** in 95% yield.[14] Hydroboration of **41** with 9-BBN gave **42** as a mixture of two epimers with D-gluco and L-idose configurations in quantitative yield.[14] This mixture was subjected to hydrogenolysis which resulted in the removal of the benzyl groups and upon acid treatment the resulting product furnished isofagomine **4A** and 5-*epi*-isofagomine **4B** in 89% yield (Scheme 5). Each of these isomers was successfully separated by silica gel chromatography with 2-propanol–water–NH_4OH (7 : 2 : 1, v/v) to afford the faster moving isofagomine **4A** and the slower moving 5-*epi*-isofagomine **4B** in a ratio of 8 : 2. Spectral data for **4A** and **4B** were in complete agreement with those reported in literature.[14,28]

Further, azasugar **10** (Fig. 2, Scheme 6) is known to be a moderate inhibitor of β-glucosidase.[29a] We realized that **41** could be easily transformed into **10**. Thus, compound **41** upon dihydroxylation using a catalytic amount of osmium tetroxide and NMO afforded a separable mixture of diastereomeric diols **43** and **44** in 9 : 1 ratio. Deprotection of the major isomer **43** was finally carried out in two steps *viz.* hydrogenolysis of benzyl groups using $Pd(OH)_2/C$–H_2 and NHBoc deprotection employing acidic conditions gave the deprotected compound **10** in 80% yield (Scheme 6). Spectral data for **10** was in complete agreement with those reported in literature.[29b]

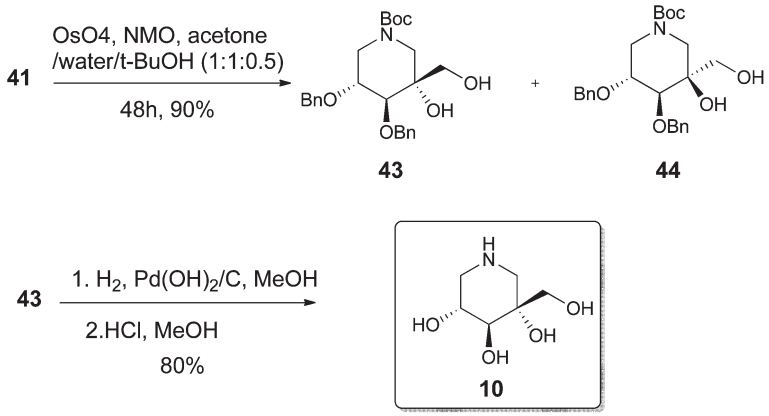
Similarly, glycosyl amide **25a/b** was transformed into 2-hydroxymethyl analogue and subsequent reactions gave the corresponding polyhydroxylated frameworks *viz.* *ent*-isogalactoisofagomine **11** and its analogue **12** and fucosidase inhibitor **6**[14] (Scheme 7) following the same sequence of reactions as employed above for manipulating compound **32**.

Conclusion

In summary, we have reported the facile aza-Claisen rearrangement of 2-*C*-hydroxymethyl glycals to prepare α/β-*N*-glycosyltrichloroacetamidates. These sugar-derived trichloroacetamidates were converted into biologically important polyhydroxylated piperidine frameworks. The synthesis of isofagomine has been achieved with modest (4 : 1) selectivity.



Scheme 5 Synthesis of isofagomine **4A** and 5-*epi*-isofagomine **4B**.



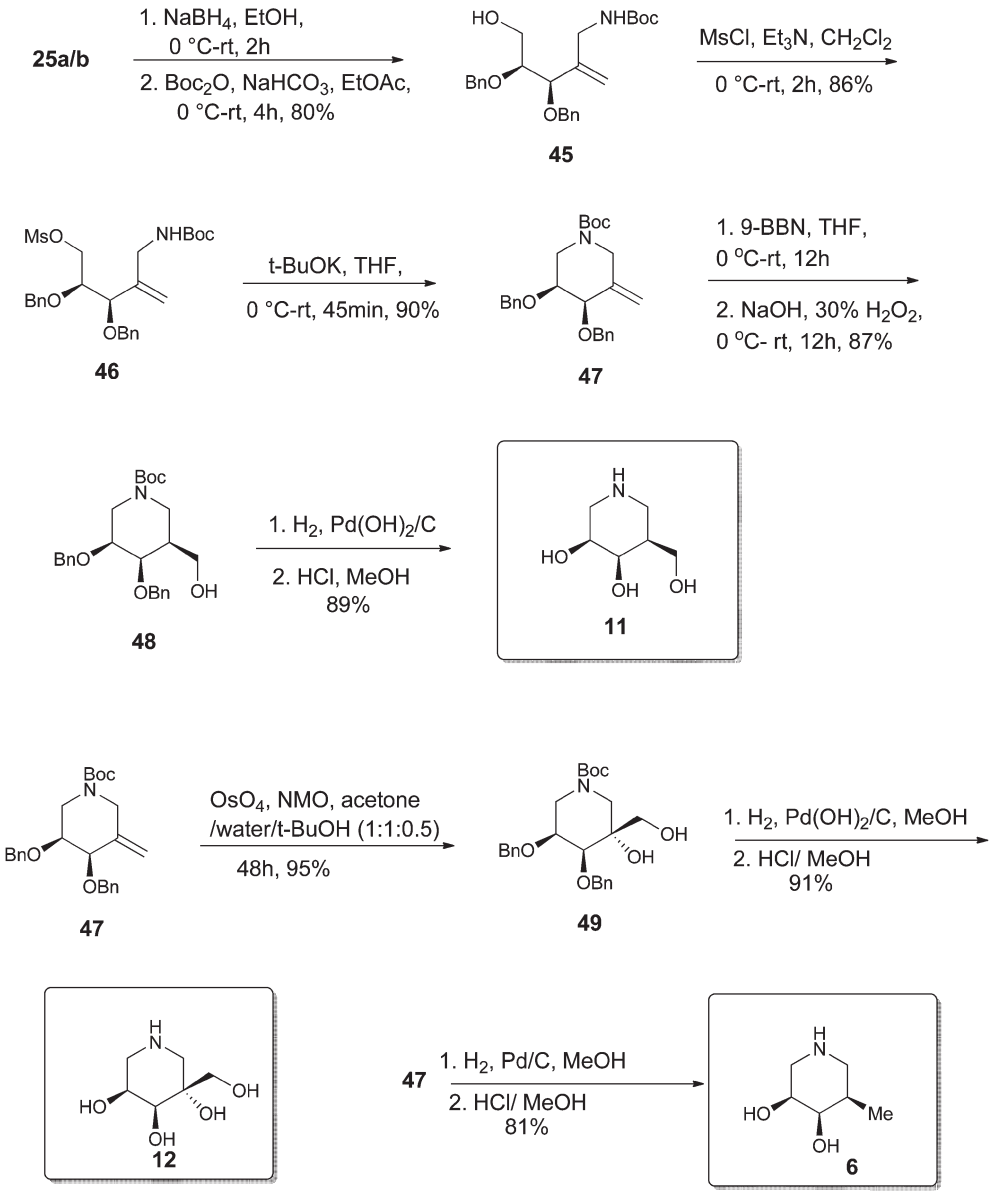
Scheme 6 Synthesis of azasugar **10**.

Experimental

Infrared spectra were recorded on Bruker FT/IR Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL LA-400 (400 and 100 MHz respectively) spectrometer or JEOL ECX-500 spectrometer (500 and 125 MHz respectively) in solutions of $CDCl_3$ using tetramethylsilane as the internal standard. The mass spectra were recorded on a Waters HAB 213 Q Tof Premier Micromass spectrometer. Optical rotations were recorded on an Autopol II automatic polarimeter at the wavelength of sodium D-line (589 nm) at 28 °C. Column chromatography was performed on silica gel (100–200 mesh) and thin layer chromatography (TLC) was performed on silica gel plates made by using grade G silica gel obtained from s.d.fine-chem Ltd., Mumbai or on Merck silica gel pre-coated plates. All solvents and common reagents were purified by established procedures.

(3*R*,4*S*)-3,4-bis(Benzyloxy)-3,4-dihydro-2H-pyran-5-carbaldehyde (19)

$POCl_3$ (5.17 g, 33.71 mmol) was added dropwise to a stirred solution of di-*O*-benzyl-D-arabinal **18** (2.5 g, 8.43 mmol) in dry DMF (30 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min at the same temperature, brought to room temperature and stirred for 18 h. After completion of the reaction (TLC monitoring) the reaction mixture was transferred to another round bottom flask containing aq. saturated sodium bicarbonate and stirred vigorously for 2 h. The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and the solvent was removed to obtain the crude vinyl aldehyde **19** which was purified column chromatography. Yield: 73% (2.01 g), R_f: 0.4 (hexane : ethyl acetate, 4 : 1), yellow liquid, $[\alpha]_D^{28}$ = +193.0 (*c* 1.0, CH_2Cl_2). IR(neat) ν_{max} cm^{-1}: 3063, 3031,



Scheme 7 Synthesis of sugar some other azasugars.

2872, 1721, 1621, 1496, 1453, 1407, 1376, 1301, 1270, 1229, 1202, 1092, 972, 939, 779, 740, 713. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.41–7.24 (m, 11H, Ar*H*, H-2), 4.75 (dd, 2H, J = 11.48 Hz, 11.72 Hz, –OC*H*Ph), 4.69–4.68 (m, 1H), 4.64 (d, 1H, J = 11.96 Hz, –OC*H*Ph), 4.49 (d, 1H, J = 11.96 Hz, –OC*H*Ph), 4.30 (t, 1H, J = 10.96 Hz), 4.23–4.19 (m, 1H), 3.68–3.63 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 166.1, 138.6, 137.4, 128.4–127.4 (m, Ar–C), 119.3, 72.2, 70.9, 64.9, 63.6 HRMS (ESI): calcd for $C_{20}H_{20}NaO_4$ $[M + Na]^+$ 347.1254; found 347.1255.

((3*R*,4*S*)-3,4-bis(Benzyloxy)-3,4-dihydro-2H-pyran-5-yl) methanol (20)

$NaBH_4$ (703 mg, 0.68 mmol) was added portionwise to a stirred solution of aldehyde **19** (1.5 g, 4.62 mmol) in dry methanol (25 mL) at 0 °C. The reaction mixture was stirred for 30 min and then quenched by the addition of saturated NH_4Cl solution (10 mL). Methanol was removed *in vacuo*, and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and the solvent was removed to obtain the crude alcohol **20** which was purified by column chromatography. Yield: 85% (1.28 g), R_f: 0.4 (hexane : ethyl acetate, 7 : 3), yellow liquid, $[\alpha]_D^{28}$ = +49.0 (c 1.0, CH_2Cl_2). IR(neat) ν_{max} cm^{-1}: 3423, 3087, 3063, 3030, 2876, 1724, 1700, 1663, 1619, 1496, 1454, 1377, 1345, 1312, 1229, 1204, 1170, 1100, 1026, 739, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.29 (m, 10H, Ar*H*), 6.42 (s, 1H), 4.94 (d, 1H, J = 11.24 Hz, –OC*H*Ph), 4.71 (s, 2H, –OC*H*Ph), 4.65 (d, 1H, J = 11.44 Hz, –OC*H*Ph), 4.23 (d, 1H, J = 3.44 Hz), 4.05–3.93 (m, 4H), 3.83–3.78 (m, 1H), 1.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 138.6, 137.9, 128.5–127.5 (m, Ar–C), 111.9, 74.2, 73.3, 71.6, 69.7, 62.8, 61.9. HRMS (ESI): calcd for $C_{20}H_{22}NaO_4$ $[M + Na]^+$ 349.1410; found 349.1417.

N-((4S,5R)-4,5-bis(Benzyloxy)-3-methylenetetrahydro-2H-pyran-2-yl)-2,2,2-trichloroacetamide (21a/b)

A solution of 2-*C*-hydroxymethyl glycal **20** (500 mg, 1.53 mmol) in dichloromethane (12 mL) was cooled to 0 °C. Trichloroacetonitrile (2.29 mmol, 332 mg) was added to it, followed by the addition of NaH (1.83 mmol, 44 mg) in small portions. The resulting mixture was stirred at 0 °C for 30 min. The cooling bath was removed and stirring continued for 12 h. The reaction mixture was quenched by adding saturated NH_4Cl solution and extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water and brine solution, dried over sodium sulfate, filtered and concentrated. Column chromatography of the crude reaction mixture afforded *N*-glycosyl trichloroacetamides **21a/b** in 88% (635 mg) Yield. α : β = 9 : 1, R_f: 0.45 (hexane : ethyl acetate, 9 : 1). IR (neat) ν_{max} cm^{-1}: 3317, 3063, 3031, 2877, 1723, 1660, 1513, 1454, 1257, 1226, 1082, 1028, 932, 840, 822, 740, 699, 678. ^1H NMR (400 MHz, $CDCl_3$, mixture of anomers): δ 8.54 (d, *J* = 8.5 Hz, 0.2H), 7.39–7.25 (m, 12H, Ar*H*), 7.00 (d, 1H, *J* = 9.04 Hz), 5.87 (d, 1H, *J* = 9.28 Hz), 5.77 (d, 0.2H, *J* = 8.56 Hz), 5.34 (s, 0.2H), 5.24 (s, 1H), 5.18 (s, 0.2H), 5.11(s, 1H), 4.74 (d, 1H, *J* = 12.44 Hz, –OC*H*Ph), 4.68 (d, 0.2H, *J* = 12.72 Hz, –OC*H*Ph), 4.58–4.55 (m, 1.2H), 4.43 (dd, 2H, *J* = 12.20 Hz, 12.44 Hz), 4.30 (d, 0.2H, *J* = 3.00 Hz), 4.27 (d, 1H, *J* = 2.92 Hz), 4.12 (t, 1H, *J* = 10.72 Hz), 4.02 (t, 0.2H, *J* = 10.72 Hz), 3.88 (dd, 1H, *J* = 10.96, 4.92 Hz), 3.80–3.75 (m, 0.2H), 3.67–3.61 (m, 0.2H), 3.60–3.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers): δ 161.3, 161.2, 137.8, 137.7, 137.6, 137.5, 136.8, 128.6–127.7 (m, Ar–C), 119.0, 114.1, 92.3, 79.0, 78.3, 77.5, 77.4, 76.0, 75.6, 75.1, 71.7, 71.3, 71.0, 69.6, 64.4, 58.6. HRMS (ESI): calcd for $C_{22}H_{22}Cl_3NNaO_4$ $[M + Na]^+$ 492.0507; found 492.0515.

((3S,4R)-3,4-bis(Benzyloxy)-3,4-dihydro-2H-pyran-5-yl) methanol (24)

Compound **24** (1.28 g, 85% yield) was obtained as a viscous liquid from **23** (1.5 g, 4.62 mmol) using the same procedure which was used to obtain **20**. R_f: 0.4 (hexane : ethyl acetate, 7 : 3), yellow liquid, $[\alpha]_D^{28}$ = −66.0 (*c* 1.25, CH_2Cl_2). IR(neat) ν_{max} cm^{-1}: 3412, 3087, 3063, 3030, 2981, 2930, 2875, 1662, 1618, 1496, 1454, 1378, 1342, 1296, 1229, 1198, 1168, 1135, 1101, 1051, 1025, 738, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39–7.25 (m, 10H, Ar*H*), 6.42 (s, 1H), 4.95 (d, 1H, *J* = 11.20 Hz, –OC*H*Ph), 4.71 (s, 2H, –OC*H*Ph), 4.66 (d, 1H, *J* = 11.45 Hz, –OC*H*Ph), 4.24 (d, 1H, *J* = 3.15 Hz), 4.04–3.93 (m, 4H), 3.83–3.79 (m, 1H), 1.68 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 138.6, 138.0, 128.6–127.7 (m, Ar–C), 111.9, 74.2, 73.9, 71.7, 69.8, 62.9, 61.9. HRMS (ESI): calcd for $C_{20}H_{22}NaO_4$ $[M + Na]^+$ 349.1410; found 349.1412.

N-((4R,5S)-4,5-bis(Benzyloxy)-3-methylenetetrahydro-2H-pyran-2-yl)-2,2,2-trichloroacetamide (25a/b)

Compound **25a/b** (635 mg, 88% yield) was obtained as a liquid from **24** (500 mg, 1.53 mmol) using the same procedure which was used to obtain **21a/b**. α : β = 9 : 1, R_f: 0.45 (hexane : ethyl acetate, 9 : 1). IR(neat) ν_{max} cm^{-1}: 3321, 3063, 3031, 2878, 1723, 1660, 1513, 1454, 1259, 1227, 1087, 1028, 932, 841, 822, 740, 699, 678. ^1H NMR (500 MHz, $CDCl_3$, mixture of anomers): δ 8.66 (d, *J* = 8.25 Hz, 0.2H), 7.39–7.28 (m, 12H, Ar*H*), 7.00 (d, 1H, *J* = 9.20 Hz), 5.87 (d, 1H, *J* = 9.20 Hz), 5.77 (d, 0.2H, *J* = 8.55 Hz), 5.33 (s, 0.2H), 5.23 (s, 1H), 5.17 (s, 0.2H), 5.10 (s, 1H), 4.73 (d, 1H, *J* = 12.55 Hz, –OC*H*Ph), 4.68 (d, 0.2H, *J* = 13.75 Hz, –OC*H*Ph), 4.58–4.55 (m, 1.2H), 4.44 (dd, 2H, *J* = 12.20 Hz, 12.25 Hz), 4.31 (d, 0.2H, *J* = 2.75 Hz), 4.27 (d, 1H, *J* = 2.75 Hz), 4.11 (t, 1H, *J* = 10.70 Hz), 4.01 (t, 0.2H, *J* = 11.00 Hz), 3.88 (dd, 1H, *J* = 11.00, 4.90 Hz), 3.80–3.75 (m, 0.2H), 3.67–3.61 (m, 0.2H), 3.60–3.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers): δ 161.5, 161.2, 140.2, 137.8, 137.6, 137.4, 136.8, 128.6–127.7 (m, Ar–C), 118.1, 114.1, 92.3, 79.0, 77.5, 77.4, 76.0, 75.9, 75.5, 75.0, 71.6, 71.3, 70.9, 69.5, 64.4, 58.6. HRMS (ESI): calcd for $C_{22}H_{22}Cl_3NNaO_4$ $[M + Na]^+$ 492.0507; found 492.0527.

((3R,4R)-3,4-bis(Benzyloxy)-3,4-dihydro-2H-pyran-5-yl) methanol (28)

Compound **28** (806 mg, 80% yield) was obtained as a viscous liquid from **27** (1.0 g, 3.08 mmol) using the same procedure which was used to obtain **20**. R_f: 0.4 (hexane : ethyl acetate, 7 : 3), yellow liquid, $[\alpha]_D^{28}$ = −70.8 (*c* 1.2, CH_2Cl_2). IR(neat) ν_{max} cm^{-1}: 3432, 3062, 3030, 2868, 1666, 1604, 1496, 1454, 1399, 1348, 1304, 1249, 1204, 1171, 1094, 1058, 1027, 1001, 928, 738, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–6.59 (m, 10H, Ar*H*), 6.60 (s, 1H), 4.66–4.51 (m, 4H), 4.15–4.12 (m, 1H), 4.06–3.93 (m, 3H), 3.87 (d, 1H, *J* = 11.60 Hz), 3.70 (s, 1H), 1.71 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 137.8, 137.6, 128.5–127.8 (m, Ar–C), 111.3, 71.8, 71.7, 71.2, 71.0, 63.7, 62.9. HRMS (ESI): calcd for $C_{20}H_{26}NO_4$ $[M + NH_4]^+$ 344.1856; found 344.1862.

N-((4R,5R)-4,5-bis(Benzyloxy)-3-methylenetetrahydro-2H-pyran-2-yl)-2,2,2-trichloroacetamide (29a/b)

Compound **29a/b** (563 mg, 78% yield) was obtained as a viscous liquid from **28** (500 mg, 1.53 mmol) using the same procedure which was used to obtain **21a/b**. α : β = 1 : 1, R_f: 0.4 (hexane : ethyl acetate, 9 : 1). IR (neat) ν_{max} cm^{-1}: 3366, 2917, 1722, 1620, 1497, 1453, 1049, 822, 738, 697, 670. ^1H NMR (500 MHz, $CDCl_3$, mixture of anomers): δ 8.43 (d, 1H, *J* = 8.25 Hz), 7.36–7.25 (m, 21H, Ar*H*, –N*H*COCl$_3$), 5.91 (d, 1H, *J* = 9.20 Hz), 5.87 (d, 1H, *J* = 8.55 Hz), 5.45 (s, 1H), 5.39 (s, 1H), 5.25 (s, 1H), 5.23 (s, 1H), 4.66–4.55 (m, 6H), 4.49 (d, 1H, *J* = 11.60 Hz, –OC*H*Ph), 4.34 (d, 1H, *J* = 11.90 Hz, –OC*H*Ph), 4.15–4.07 (m, 3H), 3.99 (dd, 2H, *J* = 9.75 Hz, 12.85 Hz), 3.81 (d, 1H, *J* = 13.10 Hz), 3.63 (br s, 1H), 3.57 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers): δ 161.4, 161.3, 139.0, 137.6, 137.6, 137.4, 136.5, 136.0, 128.7–127.6 (m, Ar–C), 119.3, 115.8, 92.5, 92.4, 79.4, 77.8, 77.4, 75.5, 74.4, 71.5, 71.3, 71.3, 71.2, 70.0, 65.8, 59.0. HRMS (ESI): calcd for $C_{22}H_{22}Cl_3NNaO_4$ $[M + Na]^+$ 492.0507; found 492.0510.

***tert*-Butyl (3S,4R)-3,4-bis(benzyloxy)-5-hydroxy-2-methylenepentylcarbamate (30)**

$NaBH_4$ (162 mg, 4.24 mmol) was added portionwise to a stirred solution of compound **21a/b** (500 mg, 1.06 mmol) in dry ethanol (10 mL) at 0 °C. The reaction mixture was stirred for 2 h

and then quenched by addition of saturated NH_4Cl solution (10 mL). Ethanol was removed *in vacuo*, and the crude reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and the solvent removed to obtain the crude amino alcohol which was subjected to subsequent reaction without any further purification. Thus, amino alcohol was taken in ethyl acetate (10 mL) and cooled to 0 °C. It was then treated with saturated $NaHCO_3$ solution (10 mL) followed by Boc_2O (0.28 mL, 1.48 mmol) and allowed the reaction mixture to stir for 4 h. It was extracted with ethyl acetate (3 × 25 mL), washed with water, brine, and dried over Na_2SO_4. Solvent evaporation followed by purification through column chromatography gave compound **30** in 80% (365 mg, over 2 steps) yield as viscous liquid. R_f: 0.5 (hexane : ethyl acetate, 3 : 2), colorless liquid, $[\alpha]_D^{28}$ = +23.7 (*c* 1.2, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3423, 3063, 3031, 2976, 2928, 2872, 1696, 1510, 1454, 1391, 1366, 1250, 1207, 1169, 1071, 1028, 911, 737, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 5.29 (s, 1H), 5.24 (s, 1H), 4.75 (br s, 1H), 4.61–4.55 (m, 3H, 3 × –OC*H*Ph), 4.31 (d, 1H, *J* = 11.60 Hz, –OC*H*Ph), 4.00 (d, 1H, *J* = 7.00 Hz), 3.75 (br s, 4H), 3.60 (br s, 1H), 2.22 (br s, 1H), 1.43 (s, 9H, –C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 143.3, 137.9, 137.7, 128.5–127.9 (m, Ar–C), 115.8, 81.1, 80.0, 79.4, 72.7, 70.8, 61.9, 42.4, 28.5. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_5$ $[M + Na]^+$ 450.2251; found 450.2255.

(2*R*,3*S*)-2,3-bis(Benzyloxy)-4-((*tert*-butoxycarbonylamino) methyl)pent-4-enyl methanesulfonate (31)

Et_3N (0.19 mL, 1.4 mmol) was added to a solution of amino alcohol **30** (300 mg, 0.70 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C. Methanesulfonyl chloride (0.08 mL, 1.05 mmol) was added dropwise to the reaction mixture and then allowed to stir for 2 h at same temperature. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. Solvent removal followed by column chromatography afforded the mesylated compound **31** (306 mg, 86%) as a colorless liquid. R_f: 0.6 (hexane : ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = +15.62 (*c* 1.6, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3418, 3064, 3031, 2977, 2933, 1710, 1510, 1454, 1391, 1356, 1249, 1174, 1092, 1027, 966, 819, 740, 699, 528. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 5.31 (s, 1H), 5.25 (s, 1H), 4.72 (br s, 1H), 4.65 (d, 1H, *J* = 11.30 Hz, –OC*H*Ph), 4.55 (dd, 2H, *J* = 11.60 Hz, 11.30 Hz, –OC*H*Ph), 4.50 (dd, 1H, *J* = 11.00 Hz, 11.00 Hz), 4.34 (dd, 1H, *J* = 5.20 Hz, 5.20 Hz), 4.30 (d, 1H, *J* = 11.30 Hz, –OC*H*Ph), 3.96 (d, 1H, *J* = 5.55 Hz), 3.74 (d, 3H, *J* = 5.80 Hz), 2.91 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 142.7, 137.4, 137.3, 128.4–127.8 (m, Ar–C), 116.2, 79.3, 79.0, 78.0, 72.9, 70.6, 68.7, 42.2, 37.4, 28.3. HRMS (ESI): calcd for $C_{26}H_{35}NNaO_7S$[M + Na]$^+$ 528.2026; found 528.2038.

(3*R*,4*S*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-methylenepiperidine-1-carboxylate (32)

Compound **31** (250 mg, 0.58 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. *t*-BuOK (130 mg, 1.16 mmol) was added to this reaction mixture. After stirring for 2 h at room temperature, it was extracted with ethyl acetate (3 × 20 mL), washed with water and brine, and dried over Na_2SO_4. Solvent evaporation followed by purification through column chromatography gave compound **32** (183 mg, 90%) as viscous liquid. R_f: 0.6 (hexane : ethyl acetate, 4 : 1), colorless liquid, $[\alpha]_D^{28}$ = +9.2 (*c* 1.3, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3064, 3031, 2976, 2930, 2871, 1694, 1454, 1416, 1367, 1257, 1231, 1204, 1164, 1119, 1069, 1027, 737, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.25 (m, 20H, Ar*H*), 5.17 (br s, 1H), 5.11 (br s, 1H), 5.02 (s, 2H), 4.63 (d, 3H, *J* = 12.50 Hz, –OC*H*Ph), 4.57 (br s, 3H, –OC*H*Ph), 4.40 (d, 2H, *J* = 12.55 Hz, –OC*H*Ph), 4.17 (br s, 1H), 4.07 (s, 3H), 3.98 (br s, 1H), 3.74–3.70 (m, 3H), 3.46–3.43 (m, 4H), 1.44 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 154.6, 139.6, 138.3, 128.4–127.6 (m, Ar–C), 115.3, 114.4, 80.0, 77.2, 75.6, 70.5, 69.6, 69.0, 45.7, 43.3, 42.0, 28.5. HRMS (ESI): calcd for $C_{25}H_{31}NNaO_4$ $[M + Na]^+$ 432.2145; found 432.2154.

(3*R*,4*S*,5*R*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-(hydroxymethyl) piperidine-1-carboxylate (33)

a 0.5 M solution of 9-BBN (1.2 mL, 1.2 mmol) in THF was added dropwise to a stirred solution of **32** (100 mg, 0.24 mmol) in THF (4 mL) at 0 °C, and the reaction mixture was stirred for 20 h at room temperature and then cooled to 0 °C. To the cooled mixture were successively added water (0.3 mL), 1 N NaOH solution (0.3 mL), and 30% H_2O_2 solution (0.3 mL) at 0 °C, and the reaction mixture stirred for 12 h at room temperature. It was diluted with water and extracted with EtOAc (3 × 15 mL). The combined extracts were successively washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel to give **33** (91 mg, 87%) as a colorless liquid. R_f: 0.5 (hexane : ethyl acetate, 1 : 1), $[\alpha]_D^{28}$ = −16.9 (*c* 1.3, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3438, 3063, 3030, 2975, 2927, 2875, 1690, 1454, 1426, 1366, 1239, 1168, 1141, 1097, 1065, 1027, 883, 736, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.25 (m, 10H, Ar*H*), 4.91–4.70 (m, 2H), 4.62 (d, 4H, *J* = 11.60 Hz, –OC*H*Ph), 3.97 (br s, 2H), 3.68 (br s, 2H), 3.50 (br s, 1H), 3.38–3.16 (m, 1H), 1.90–1.80 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 138.5, 138.2, 128.3–127.2 (m, Ar–C), 79.8, 75.3, 73.2, 72.8, 71.0, 62.2, 61.2, 43.7, 41.8, 28.3. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_5$ $[M + Na]^+$ 450.2251; found 450.2258.

((3*R*,4*S*,5*R*)-4,5-bis(Benzyloxy)piperidin-3-yl)methyl acetate (34)

Ac_2O (0.01 mL, 0.16 mmol), Et_3N (0.02 mL, 0.16 mmol) and a catalytic amount of DMAP were added to a stirred solution of compound **33** (50 mg, 0.11 mmol) in dry CH_2Cl_2 (4 mL) cooled to 0 °C. After stirring for 2 h at room temperature, the usual workup and chromatographic purification afforded the corresponding acetate which was directly used for further reaction. The residue was taken in CH_2Cl_2 (1 mL), cooled to 0 °C and trifluroacetic acid (0.05 mL) was added. After stirring for 2 h, the reaction mixture was neutralized with aq. Na_2CO_3 solution, and extracted with CH_2Cl_2 (3 × 10 mL). Purification through column chromatography afforded pure compound **34** (35 mg, 81%) as a colourless liquid. R_f: 0.2 (ethyl acetate) $[\alpha]_D^{28}$ = −6.45

(*c* 1.55, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3441, 3063, 3030, 2924, 2854, 1739, 1606, 1496, 1453, 1367, 1245, 1093, 1064, 1028, 737, 699. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 4.88 (d, 1H, *J* = 11.15 Hz, –OC*H*Ph), 4.66 (s, 2H, –OC*H*Ph), 4.58 (d, 1H, *J* = 11.70 Hz, –OC*H*Ph), 4.10 (br s, 2H, H-7, H-7′), 3.92 (br s, 1H, H-4), 3.55–3.53 (m, 1H, H-5), 3.08 (dd, 1H, *J* = 9.45 Hz, 9.15 Hz, H-6), 2.98–2.96 (m, 1H, H-6′), 2.79 (t, 1H, *J* = 10.30 Hz, H-2), 2.72 (dd, 1H, *J* = 4.00 Hz, 8.35 Hz, H-2′), 2.63 (s, 1H, H-1), 2.00–1.95 (m, 4H, H-3, –OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 138.7, 138.4, 128.4–127.3 (m, Ar–C), 78.3, 74.4, 73.2, 71.2, 63.1, 45.2, 43.2, 40.3, 29.6, 20.9. HRMS (ESI): calcd for $C_{22}H_{28}NO_4$ $[M + H]^+$ 370.2013; found 370.2018.

(3*S*,4*R*,5*R*)-*tert*-Butyl 4,5-bis(benzyloxy)-3-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate (35)

To a stirred solution of compound **32** (200 mg, 0.48 mmol) in acetone : water: *t*-BuOH (4 mL, 1 : 1 : 0.5) at room temperature were added NMO (66 mg, 0.56 mmol) and OsO_4 (25 mg mL^{-1} solution in *t*-BuOH, 0.02 mL, 0.002 mmol). The reaction mixture was stirred for 48 h and then treated with $Na_2S_2O_5$ (106 mg, 0.56 mmol). The reaction mixture was stirred for further 0.5 h and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water and finally with brine. Evaporation of the organic layer followed by purification through column chromatography gave compound **35** (206 mg, 95%). R_f: 0.5 (hexane : ethyl acetate, 1 : 1), white solid, $[\alpha]_D^{28}$ = −32.25 (*c* 1.55, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3432, 3088, 3064, 3029, 3005, 2975, 2929, 1670, 1495, 1455, 1429, 1367, 1306, 1272, 1239, 1209, 1163, 1118, 1090, 1073, 1041, 1027, 879, 737, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 4.79 (d, 1H, *J* = 11.30 Hz, −OC*H*Ph), 4.64–4.57 (m, 3H, 3 × –OC*H*Ph), 3.83 (br s, 2H), 3.71 (br d, 4H, *J* = 14.00 Hz), 3.50 (br s, 2H), 3.26 (br s, 1H), 3.01 (br s, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 155.6, 138.4, 138.1, 128.3–127.2 (m, Ar–C), 80.3, 79.4, 79.3, 79.2, 74.3, 74.0, 73.6, 73.2, 73.1, 71.1, 65.6, 64.7, 47.0, 44.3, 28.4. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_6$ $[M + Na]^+$ 466.2200; found 466.2205.

(3*R*,4*R*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-oxopiperidine-1-carboxylate (36)

$NaIO_4$ (106 mg, 0.49 mmol) dissolved in water was added to a solution of diol **35** (150 mg, 0.33 mmol) in methanol (3 ml) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. Water was added to the reaction mixture and solvent evaporated *in vacuo*. The residue was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine and concentrated. The residual oil was purified by silica gel chromatography to give the ketone **36** (134 mg, 96%) as a colorless liquid. R_f: 0.7 (hexane : ethyl acetate, 7 : 3), $[\alpha]_D^{28}$ = +15.55 (*c* 1.35, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3064, 3032, 2977, 2931, 1739, 1698, 1455, 1395, 1368, 1251, 1206, 1156, 1027, 738, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.35–7.25 (m, 20H, Ar*H*), 4.90 (dd, 2H, *J* = 12.50 Hz, 11.95 Hz), 4.74–4.64 (m, 4H, 4 × –OC*H*Ph), 4.67 (d, 2H, *J* = 11.60 Hz, 2 × –OC*H*Ph), 4.29 (br d, 2H, *J* = 18.30 Hz), 4.18–4.10 (m, 4H), 3.90 (d, 2H, *J* = 13.75 Hz), 3.76 (d, 2H, *J* = 12.50 Hz, 2 × –OC*H*Ph), 3.64 (t, 2H, *J* = 14.40 Hz), 1.43 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 154.5, 137.5, 137.2, 128.4–127.6 (m, Ar–C), 82.5, 82.3, 80.9, 80.8, 74.3, 73.8, 72.5, 72.4, 71.9, 71.7, 53.4, 52.3, 47.4, 46.0, 28.2. HRMS (ESI): calcd for $C_{24}H_{29}NNaO_5$ $[M + Na]^+$ 434.1938; found 434.1945.

(3*S*,4*R*,5*R*)-*tert*-Butyl 3-acetoxy-4,5-bis(benzyloxy)piperidine-1-carboxylate (37)

To a stirred solution of compound **36** (100 mg, 0.24 mmol) in methanol (3 mL) cooled to 0 °C was added $NaBH_4$ (14 mg, 0.36 mmol). The reaction mixture was stirred at same temperature for 30 min and then quenched with saturated NH_4Cl solution. The reaction mixture was concentrated under high vacuum to remove methanol. Aqueous phase was extracted with ethyl acetate (3 × 10 mL), combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After concentration, crude residue was directly subjected to acetylation in dry CH_2Cl_2 (2 mL) using Ac_2O, Et_3N and a catalytic amount of DMAP. After stirring for 4 h at room temperature, usual workup and chromatographic purification afforded acetate **37** (100 mg, 90%) as a colorless liquid. R_f: 0.6 (hexane : ethyl acetate, 3 : 1), $[\alpha]_D^{28}$ = −12.94 (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3064, 3030, 2976, 2930, 1739, 1697, 1496, 1454, 1417, 1367, 1320, 1229, 1167, 1100, 1047, 1028, 987, 953, 911, 882, 738, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.25 (m, 10H, Ar*H*), 4.84 (d, 1H, *J* = 11.96 Hz, –OC*H*Ph), 4.70–4.55 (m, 4H), 4.12 (br s, 1H), 3.95–3.82 (m, 1H), 3.46 (br s, 3H), 3.25–3.10 (m, 1H), 2.01 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 154.8, 138.8, 138.1, 128.5–127.4 (m, Ar–C), 80.3, 75.5, 74.8, 74.7, 74.1, 71.2, 69.7, 41.2, 28.4, 21.1. HRMS (ESI): calcd for $C_{26}H_{33}NNaO_6$ $[M + Na]^+$ 478.2206; found 478.2208.

(3*S*,4*R*,5*R*)-4,5-bis(Benzyloxy)piperidin-3-yl acetate (38)

Compound **38** (32 mg, 82% yield) was obtained from **37** (50 mg, 0.10 mmol) using the procedure which was used to obtain **34**. R_f: 0.2 (ethyl acetate), $[\alpha]_D^{28}$ = +25.33 (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3329, 3063, 3030, 2930, 2867, 1738, 1496, 1453, 1365, 1242, 1160, 1095, 1048, 1028, 981, 946, 738, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.25 (m, 10H, Ar*H*), 4.80 (d, 1H, *J* = 12.05 Hz, –OC*H*Ph), 4.73–4.69 (m, 2H, H-2, H-3), 4.69–4.55 (m, 3H, –OC*H*Ph) 4.05 (br s, 1H, H-1), 3.47 (br s, 1H, H-5), 3.05–3.00 (m, 2H, H-2′, H-6′), 2.03 (s, 3H, –OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 138.8, 138.3, 128.6–127.3 (m, Ar–C), 75.2, 73.6, 73.4, 71.2, 71.0, 44.8, 44.3, 21.1. HRMS (ESI): calcd for $C_{21}H_{26}NO_4$ $[M + H]^+$ 356.1856; found 356.1860.

tert-Butyl (3*R*,4*R*)-3,4-bis(benzyloxy)-5-hydroxy-2-methylenepentylcarbamate (39)

Compound **39** (355 mg, 78% yield) was obtained as a colorless liquid from **29a/b** (500 mg, 1.06 mmol) using the same procedure which was used to obtain **30**. R_f: 0.5 (hexane : ethyl

acetate, 3 : 1), colorless liquid, $[\alpha]_D^{28} = -9.4$ (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3423, 3063, 3030, 2976, 2929, 2871, 1696, 1511, 1454, 1391, 1281, 1251, 1169, 1088, 1071, 1028, 912, 736, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.25 (m, 10H, Ar*H*), 5.23 (d, 2H, *J* = 13.75 Hz), 4.81 (d, 2H, *J* = 11.65 Hz), 4.65 (d, 1H, *J* = 11.65 Hz), 4.59 (d, 1H, *J* = 11.60 Hz), 4.35 (d, 1H, *J* = 11.90 Hz), 4.04 (d, 1H, *J* = 6.40 Hz), 3.77–3.51 (m, 5H), 2.22 (br s, 1H), 1.43 (s, 9H, –C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 142.8, 138.2, 137.9, 128.4–127.7 (m, Ar–C), 115.1, 82.9, 80.7, 79.4, 73.7, 70.8, 61.9, 42.0, 28.3. HRMS (ESI): calcd for $C_{25}H_{34}NO_5$ $[M + H]^+$ 428.2431; found 428.2435.

(2*R*,3*R*)-2,3-bis(Benzyloxy)-4-((*tert*-butoxycarbonylamino) methyl)pent-4-enyl methanesulfonate (40)

Compound **40** (313 mg, 88% yield) was obtained as a colorless liquid from **39** (300 mg, 0.7 mmol) using the same procedure which was used to obtain **31**. R_f: 0.6 (hexane : ethyl acetate, 3 : 1), $[\alpha]_D^{28} = -2.97$ (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3396, 2922, 2851, 1592, 1461, 1384, 1119, 1092, 1037. ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.25 (m, 10H, Ar*H*), 5.24 (d, 2H, *J* = 11.00 Hz), 4.71 (dd, 2H, *J* = 11.60 Hz, 11.30 Hz), 4.59 (d, 1H, *J* = 11.95 Hz), 4.33 (d, 2H, *J* = 11.60 Hz), 4.20–4.16 (m, 1H), 4.02 (d, 1H, *J* = 5.80 Hz), 3.87 (br s, 1H), 3.75–3.72 (m, 2H), 2.89 (s, 3H), 1.43 (s, 9H, –C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 142.5, 137.7, 128.5–127.9 (m, Ar–C), 115.4, 80.7, 79.6, 78.3, 74.2, 71.1, 69.7, 42.1, 37.3, 28.4. HRMS (ESI): calcd for $C_{26}H_{35}NNaO_7S$ $[M + Na]^+$ 528.2026; found 528.2032.

(3*R*,4*R*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-methylenepiperidine-1-carboxylate (41)

Compound **41** (192 mg, 95% yield) was obtained as a colorless liquid from **40** (250 mg, 0.58 mmol) using the same procedure which was used to obtain **32**. R_f: 0.55 (hexane : ethyl acetate, 4 : 1), colorless liquid, $[\alpha]_D^{28} = +5.8$ (*c* 1.15, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3064, 3031, 2976, 2929, 1694, 1454, 1420, 1366, 1236, 1165, 1123, 1072, 1028, 913, 872, 737, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.34–7.25 (m, 20H, Ar*H*), 5.25 (br s, 2H), 5.12 (br s, 2H), 4.70 (br s, 2H, –OC*H*Ph), 4.60 (d, 2H, *J* = 11.95 Hz, –OC*H*Ph), 4.57 (d, 2H, *J* = 11.95 Hz, –OC*H*Ph), 4.45 (br s, 2H, –OC*H*Ph), 4.19–4.11 (m, 2H), 3.95–3.86 (m, 4H), 3.76–3.71 (m, 2H), 3.54 (br s, 4H), 1.43 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 138.2, 138.1, 128.3–127.5 (m, Ar–C), 115.1, 114.9, 80.0, 79.7, 71.1, 70.9, 47.9, 46.8, 43.9, 42.7, 28.3. HRMS (ESI): calcd for $C_{25}H_{32}NO_4$ $[M + H]^+$ 410.2326; found 410.2338.

(3*R*,4*R*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-(hydroxymethyl) piperidine-1-carboxylate (42)

Compound **42** (104 mg, quantitative, concomitant with **42′**) was obtained as a colorless liquid from **41** (100 mg, 0.24 mmol) using the same procedure which was used to obtain **33**. R_f: 0.5 (hexane : ethyl acetate, 1 : 1). IR (neat) ν_{max} cm^{-1}: 3447, 3063, 3030, 2975, 2927, 2875, 1692, 1495, 1453, 1426, 1392, 1366, 1314, 1249, 1158, 1097, 1027, 895, 736, 698. ^1H NMR (400 MHz, $CDCl_3$, rotameric mixture of **42** and **42′**): δ 7.36–7.25 (m, 10H, Ar*H*), 4.90–4.80 (m, 1H), 4.71–4.64 (m, 2H), 4.58 (d, 1H, *J* = 11.72 Hz, –OC*H*Ph), 3.80–3.47 (m, 8H), 1.90–1.69 (m, 2H), 1.43 (br s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, rotameric mixture of **42** and **42'**): δ 155.2, 155.4, 138.2, 138.0, 128.5–127.6 (m, Ar–C), 80.0, 79.8, 78.8, 79.7, 77.8, 73.5, 72.1, 71.7, 61.6, 61.1, 44.8, 44.5, 42.9, 42.6, 42.2, 41.3, 38.4, 28.3, 14.1. HRMS (ESI): calcd for $C_{25}H_{34}NO_5$ $[M + H]^+$ 428.2431; found 428.2437.

(4*S*,5*R*)-*tert*-Butyl 4,5-bis(benzyloxy)-3-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate

Compound **43** (89 mg, 82%) and compound **44** (10 mg, 10%) were obtained from **41** (100 mg, 0.24 mmol) using the procedure which was used to obtain **35**.

(3*R*,4*S*,5*R*)-*tert*-Butyl 4,5-bis(benzyloxy)-3-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate (43)

(Major isomer) R_f: 0.5 (hexane : ethyl acetate, 1 : 1), viscous liquid, $[\alpha]_D^{28} = -18.82$ (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3467, 3063, 3031, 2975, 2925, 2690, 1455, 1427, 1393, 1366, 1274, 1249, 1167, 1144, 1094, 1028, 888, 736, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.34–7.25 (m, 20H, Ar*H*), 4.81(d, 1H, *J* = 11.00 Hz, –OC*H*Ph), 4.68 (br s, 1H), 4.61 (br s, 4H), 4.51(d, 1H, *J* = 10.70 Hz, –OC*H*Ph), 4.44 (d, 1H, *J* = 11.00 Hz, –OC*H*Ph), 4.28 (br s, 3H), 3.95 (br s, 1H), 3.87 (d, 1H, *J* = 12.20 Hz, –OC*H*Ph), 3.68–3.62 (m, 8H), 3.52–3.35 (m, 2H), 3.21–3.10 (m, 3H), 2.48 (br s, 1H), 2.24 (br s, 1H), 1.45 (br s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 155.6, 137.9, 137.7, 137.1, 128.6–127.9 (m, Ar–C), 127.6, 80.1, 80.1, 77.2, 76.1, 74.2, 73.9, 73.7, 73.6, 73.4, 72.6, 71.6, 71.3, 65.1, 64.5, 48.2, 47.1, 43.4, 41.0, 28.4. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_6$ $[M + Na]^+$ 466.2200; found 466.2202.

(3*S*,4*S*,5*R*)-*tert*-Butyl 4,5-bis(benzyloxy)-3-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate (44)

(Minor isomer) R_f: 0.3 (hexane : ethyl acetate, 1 : 1), viscous liquid, $[\alpha]_D^{28} = -12.41$ (*c* 0.45, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3436, 3063, 3030, 2975, 2927, 1682, 1455, 1430, 1392, 1366, 1252, 1164, 1099, 1028, 897, 844, 817, 737, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.36–7.25 (m, 20H, Ar*H*), 4.78–4.75 (m, 2H), 4.65–4.28 (m, 10H), 3.76–3.33 (m, 12H), 2.77 (br s, 1H), 2.68 (br s, 1H), 1.93 (br s, 1H), 1.78 (br s, 1H), 1.44 (br s, 9H), 1.40 (br s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 155.6, 137.8, 137.6, 128.5–127.3 (m, Ar–C), 80.1, 78.7, 75.1, 74.3, 73.5, 72.0, 71.5, 70.2, 65.7, 65.1, 64.6, 64.1, 48.5, 47.0, 44.3, 44.3, 28.2. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_6$ $[M + Na]^+$ 466.2200; found 466.2209.

tert-Butyl (3*R*,4*S*)-3,4-bis(benzyloxy)-5-hydroxy-2-methylenepentylcarbamate (45)

Compound **45** (365 mg, 80% yield, over 2 steps) was obtained as a viscous liquid from **25a/b** (500 mg, 1.06 mmol) using the

same procedure which was used to obtain **30**. R_f: 0.5 (hexane : ethyl acetate, 3 : 2), colorless liquid, $[\alpha]_D^{28} = -17.0$ (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3423, 3063, 3031, 2976, 2927, 2871, 1696, 1510, 1500, 1454, 1391, 1366, 1250, 1207, 1169, 1071, 1028, 911, 737, 698. ^1H NMR (500MHz, $CDCl_3$): δ 7.33–7.25 (m, 10H, Ar*H*), 5.28 (s, 1H), 5.24 (s, 1H), 4.76 (br s, 1H), 4.61–4.56 (m, 3H, 3x-OC*H*Ph), 4.31 (d, 1H, *J* = 11.65 Hz, –OC*H*Ph), 4.00 (d, 1H, *J* = 7.00 Hz), 3.75 (br s, 4H), 3.60 (br s, 1H), 2.23 (br s, 1H), 1.43 (s, 9H, –C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 143.3, 138.0, 137.7, 128.5–127.4 (m, Ar–C), 115.9, 81.1, 80.0, 79.4, 72.7, 70.8, 61.9, 42.4, 28.5. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_5$ $[M + Na]^+$ 450.2251; found 450.2203.

(2*S*,3*R*)-2,3-bis(Benzyloxy)-4-((*tert*-butoxycarbonylamino) methyl)pent-4-enyl methanesulfonate (46)

Compound **46** (306 mg, 86% yield) was obtained as a yellow liquid from **45** (300 mg, 0.70 mmol) using the same procedure which was used to obtain **31**. R_f: 0.6 (hexane : ethyl acetate, 3 : 2), $[\alpha]_D^{28} = -18.18$ (*c* 0.55, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3421, 3064, 3031, 2977, 2933, 1710, 1505, 1454, 1391, 1357, 1249, 1210, 1174, 1075, 1051, 1027, 967, 819, 740, 699, 528. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 5.31 (s, 1H), 5.25 (s, 1H), 4.72 (br s, 1H), 4.65 (d, 1H, *J* = 11.30 Hz, –OC*H*Ph), 4.55 (dd, 2H, *J* = 11.30 Hz, 11.30 Hz, –OC*H*Ph), 4.50 (dd, 1H, *J* = 11.00 Hz, 11.00 Hz), 4.34 (dd, 1H, *J* = 5.20 Hz, 5.20 Hz), 4.30 (d, 1H, *J* = 11.30 Hz, –OC*H*Ph), 3.96 (d, 1H, *J* = 5.50 Hz), 3.74 (d, 3H, *J* = 5.80 Hz), 2.91 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 142.8, 137.4, 137.3, 128.4–127.8 (m, Ar–C), 116.2, 79.3, 79.0, 78.1, 73.0, 70.7, 68.7, 42.2, 37.4, 28.3. HRMS (ESI): calcd for $C_{26}H_{36}NO_7S[M + H]^+$ 506.2207; found 506.2214.

(3*S*,4*R*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-methylenepiperidine-1-carboxylate (47)

Compound **47** (183 mg, 90% yield) was obtained as a liquid from **46** (250 mg, 0.58 mmol) using the same procedure which was used to obtain **32**. R_f: 0.6 (hexane : ethyl acetate, 4 : 1), colorless liquid, $[\alpha]_D^{28} = -7.8$ (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3064, 3031, 2976, 2930, 2871, 1694, 1454, 1416, 1367, 1257, 1231, 1204, 1164, 1119, 1069, 1027, 737, 698. ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ 7.37–7.25 (m, 20H, Ar*H*), 5.17 (br s, 1H), 5.11 (br s, 1H), 5.02 (s, 2H), 4.63 (d, 3H, *J* = 12.55 Hz, –OC*H*Ph), 4.56 (br s, 3H, –OC*H*Ph), 4.40 (d, 2H, *J* = 12.50 Hz, –OC*H*Ph), 4.17 (br s, 1H), 4.07 (s, 3H), 3.98 (br s, 1H), 3.74–3.70 (m, 3H), 3.46–3.44 (m, 4H), 1.44 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 154.5, 139.5, 139.2, 138.1, 128.2–127.5 (m, Ar–C), 115.2, 114.4, 79.8, 77.2, 75.4, 70.4, 69.4, 46.8, 45.6, 43.2, 42.2, 28.3. HRMS (ESI): calcd for $C_{25}H_{31}NNaO_4$ $[M + Na]^+$ 432.2145; found 432.2156.

(3*S*,4*R*,5*S*)-*tert*-Butyl 3,4-bis(benzyloxy)-5-(hydroxymethyl) piperidine-1-carboxylate (48)

Compound **48** (91 mg, 87% yield) was obtained as a colorless liquid from **47** (100 mg, 0.24 mmol) using the same procedure which was used to obtain **33**. R_f: 0.5 (hexane : ethyl acetate, 1 : 1), $[\alpha]_D^{28} = +22.3$ (*c* 0.65, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3438, 3063, 3030, 2975, 2927, 2875, 1690, 1454, 1426, 1366, 1239, 1168, 1141, 1097, 1065, 1027, 883, 736, 698. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.25 (m, 10H, Ar*H*), 4.93–4.69 (m, 2H), 4.62 (d, 4H, *J* = 11.72 Hz, –OC*H*Ph), 3.97 (br s, 2H), 3.68 (br s, 2H), 3.50 (br s, 1H), 3.38–3.16 (m, 1H), 1.90–1.80 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 138.7, 138.3, 128.5–127.4 (m, Ar–C), 80.0, 75.5, 73.3, 72.9, 71.2, 62.5, 61.4, 43.8, 41.9, 28.4. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_5$ $[M + Na]^+$ 428.2431; found 428.2437.

(3*R*,4*S*,5*S*)-*tert*-Butyl 4,5-bis(benzyloxy)-3-hydroxy-3-(hydroxymethyl)piperidine-1-carboxylate (49)

Compound **49** (206 mg, 95% yield) was obtained as a white solid from **47** (200 mg, 0.48 mmol) using the same procedure which was used to obtain **35**. R_f: 0.5 (hexane : ethyl acetate, 1 : 1), white solid, $[\alpha]_D^{28} = +34.48$ (*c* 1.45, CH_2Cl_2). IR (neat) ν_{max} cm^{-1}: 3423, 3088, 3063, 3030, 2975, 2928, 1670, 1455, 1429, 1367, 1272, 1240, 1208, 1163, 1118, 1092, 1044, 1027, 881, 736, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.25 (m, 10H, Ar*H*), 4.78 (d, 1H, *J* = 11.44 Hz, –OC*H*Ph), 4.64–4.58 (m, 3H, 3x-OC*H*Ph), 3.83 (br s, 2H), 3.74–3.69 (m, 4H), 3.48 (br s, 2H), 3.19 (br s, 1H), 2.93 (br s, 1H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 155.6, 138.4, 138.1, 128.3–127.2 (m, Ar–C), 80.7, 79.4, 79.3, 79.2, 74.3, 74.0, 73.6, 73.2, 73.1, 71.6, 71.2, 65.7, 64.7, 48.5, 47.0, 43.3, 42.7, 28.4. HRMS (ESI): calcd for $C_{25}H_{33}NNaO_6$ $[M + Na]^+$ 466.2200; found 466.2207.

(3R,4R)-5-(Hydroxymethyl)piperidine-3,4-diol

Hydrogenolysis (20% $Pd(OH)_2/C$) of **42** (150 mg, 0.35 mmol) in methanol gave debenzylated compound, which was passed through a pad of Celite and the filtrate concentrated. The residue was dissolved in methanol (2 mL) and added conc. HCl (0.15 mL) to it and stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was concentrated and the residue chromatographed on silica gel with 2-propanol–H_2O–NH_4OH (7 : 2 : 1) to give pure **4A** and **4B** in 8 : 2 ratio respectively (89%, combined yield).

(3*R*,4*R*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol (4A)

Major isomer (70%, 36 mg), (R_f 0.37 in 2-propanol–H_2O–NH_4OH, 7 : 2 : 1), $[\alpha]_D^{28} = +13.3$ (*c* 1.5, CH_3OH), lit.[28] $[\alpha]_D^{25} = +25.4$ (*c* 1.30, EtOH). ^1H NMR (500 MHz, D_2O): δ 3.63 (br s, 1H), 3.51–3.41 (m, 2H), 3.22 (t, *J* = 8.90 Hz, 1H), 3.11 (m, 2H), 2.43 (m, 1H), 1.63 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.7, 70.6, 59.9, 48.3, 45.7, 43.1. HRMS calcd for $C_6H_{14}NO_3$ $[M + H]^+$ 148.0968, found: 148.0976.

(3*R*,4*R*,5*S*)-5-(Hydroxymethyl)piperidine-3,4-diol (4B)

Minor isomer (19%, 10 mg), (R_f 0.26 in 2-propanol–H_2O–NH_4OH, 7 : 2 : 1), $[\alpha]_D^{28} = -5.0$ (*c* 0.5, CH_3OH), lit.[30] $[\alpha]_D^{20} = -10.3$ (*c* 0.5, MeOH). ^1H NMR (500 MHz, D_2O): δ 3.91

(s, 1H), 3.85 (s, 1H), 3.58–3.43 (m, 2H), 3.19 (dd, 1H, J = 13.70, 13.15 Hz, 1H), 3.10 (d, 1H, J = 12.90 Hz, 1H), 2.88–2.82 (m, 1H), 2.27–2.24 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.2, 65.1, 60.2, 44.2, 40.6, 34.9. HRMS calcd for $C_6H_{14}NO_3$ $[M + H]^+$ 148.0968, found: 148.0972.

(3*R*,4*S*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol (5)

A solution of **33** (75 mg, 0.17 mmol) in methanol (5 mL) was stirred under H_2 in the presence of 20% $Pd(OH)_2$–C (35 mg) for 36 h. After completion of the reaction, the reaction mixture was filtered through the pad of Celite and the filtrate concentrated. The residue was dissolved in methanol (2 mL), added conc. HCl (0.15 mL) and stirred for 8 h. After completion of the reaction, the reaction mixture was concentrated and the residue passed through Dowex (50×) basic resin column and concentrated under reduced pressure to get the azasugar **5** (23 mg, 89% yield) as a viscous liquid. R_f: 0.2 (ethyl acetate : methanol, 4 : 1), $[\alpha]_D^{28}$ = + 2.35 (c 1.7, MeOH), lit.[31] $[\alpha]_D^{22}$ = +2.5 (c 1.0, H_2O). ^{1}H NMR (500 MHz, D_2O): δ 3.93 (br s, 1H, H-4), 3.76–3.72 (m, 1H, H-3), 3.53 (dd, 1H, J = 6.70, 11.30 Hz, H-7), 3.43 (dd, 1H, J = 7.35, 11.00 Hz, H-7′), 3.06–2.98 (m, 2H, H-2, H-6), 2.82 (t, 1H, J = 11.95 Hz, H-6′), 2.67 (t, 1H, J = 12.50 Hz, H-2′), 1.93–1.89 (m, 1H, H-5). ^{13}C NMR (125 MHz, D_2O): δ 66.0, 65.7, 60.0, 42.1, 39.7, 39.1. HRMS (ESI): calcd for $C_6H_{14}NO_3$ $[M + H]^+$ 148.0968; found 148.0973.

(3*R*,4*S*,5*S*)-5-Methylpiperidine-3,4-diol (6)

To a stirred solution of compound **47** (50 mg, 0.12 mmol) in methanol was initially treated with 10% Pd–C (5 mg) under hydrogen atmosphere. After stirring for 3 h additional amount of 10% Pd–C (30 mg) was added and stirring continued for 24 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and filtrate concentrated. The residue was dissolved in methanol (2 mL), treated with conc. HCl (0.15 mL) and stirred for 8 h. After completion of the reaction, reaction mixture was concentrated and the residue was passed through Dowex (50×) basic resin column and concentrated under reduced pressure to get the azasugar **6** (13 mg, 81% yield) as a white liquid. R_f: 0.4 (ethyl acetate : methanol, 4 : 1), $[\alpha]_D^{28}$ = −3.75 (c 0.65, MeOH), lit.[15] $[\alpha]_D^{20}$ = −6.3 (c 0.75, H_2O). ^{1}H NMR (500 MHz, D_2O): δ 3.85–3.82 (m, 1H, H-3), 3.81 (s, 1H, H-4), 3.12 (dd, 1H, J = 4.30 Hz, 12.30 Hz, H-2), 2.96 (dd, 1H, J = 4.25 Hz, 12.60 Hz, H-2′), 2.87 (t, 1H, J = 11.45 Hz, H-6), 2.69 (t, 1H, J = 12.60 Hz, H-6′) 1.94–1.89 (m, 1H, H-5), 0.90 (d, 3H, J = 6.85 Hz, H-7).^{13}C NMR (125 MHz, D_2O): δ 69.3, 65.9, 42.8, 41.5, 31.5, 13.5. HRMS (ESI): calcd for $C_6H_{13}NaO_2$ $[M + Na]^+$ 154.0838; found 154.0845.

(3*R*,4*S*,5*S*)-Piperidine-3,4,5-triol hydrochloride (7)

Hydrogenolysis (20% $Pd(OH)_2$–C) of **37** (75 mg, 0.16 mmol) in methanol gave debenzylated compound, which was passed through a pad of Celite, and the filtrate was concentrated to obtain a residue. It was dissolved in 6 N aqueous HCl (3 mL) and stirred for 4 h. Solvent removal afforded **7** (24 mg, 86%). R_f: 0.4 (ethyl acetate : methanol, 4 : 1), $[\alpha]_D^{28}$ = 0.0 (c 0.8, MeOH), lit.[26d] $[\alpha]_D^{20}$ = 0.0 (c 0.8, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 3.97–3.96 (m, 2H), 3.92 (br s, 1H), 3.15–3.07 (m, 4H). ^{13}C NMR (125 MHz, D_2O): δ 68.2, 65.4, 44.1. HRMS (ESI): calcd for $C_5H_{12}NO_3$ $[M + H]^+$ 134.0812; found 134.0818.

(3*S*,4*R*,5*R*)-3-(Hydroxymethyl)piperidine-3,4,5-triol (8)

Compound **8** (25 mg, 91% yield) was obtained as a viscous liquid from **35** (75 mg, 0.17 mmol) using the same procedure which was used to obtain **5**. R_f: 0.3 (iPrOH : H_2O : NH_4OH 7 : 2 : 1), $[\alpha]_D^{28}$ = −15.83 (c 1.2, MeOH). ^{1}H NMR (400 MHz, D_2O): δ 4.08–4.05 (m, 1H, H-3), 3.72 (br s, 1H, H-4), 3.52 (d, 1H, J = 11.90 Hz, H-6), 3.44 (d, 1H, J = 12.20 Hz, 1H, H-6′), 3.04–3.01 (dd, 1H, J = 4.90, 11.90 Hz, H-2), 2.85 (s, 2H, H-7, H-7′), 2.78 (t, 1H, J = 12.25 Hz, H-2′). ^{13}C NMR (125 MHz, D_2O): δ 72.8, 68.4, 63.8, 63.4, 44.4, 42.5. HRMS (ESI): calcd for $C_6H_{14}NO_4$ $[M + H]^+$ 164.0917; found 164.0924.

(3*S*,4*R*,5*R*)-5-Methylpiperidine-3,4-diol (9)

Compound **9** (13 mg, 81% yield) was obtained as a viscous liquid from **32** (50 mg, 0.12 mmol) using the same procedure which was used to obtain **6**. R_f: 0.4 (ethyl acetate : methanol, 4 : 1), $[\alpha]_D^{28}$ = −1.05 (c 0.65, MeOH), ^{1}H NMR (500 MHz, D_2O): δ 3.85–3.81 (m, 2H, H-3, H-4), 3.12 (dd, 1H, J = 4.30 Hz, 12.30 Hz, H-2), 2.96 (dd, 1H, J = 4.25 Hz, 12.60 Hz, H-2′), 2.87 (t, 1H, J = 11.45 Hz, H-6), 2.69 (t, 1H, J = 12.60 Hz, H-6′) 1.94–1.89 (m, 1H, H-5), 0.90 (d, 3H, J = 6.85 Hz, H-7).^{13}C NMR (125 MHz, D_2O): δ 69.3, 65.9, 42.8, 41.5, 31.5, 13.5. HRMS (ESI): calcd for $C_6H_{14}NO_2$ $[M + H]^+$ 132.1019; found 132.1027.

(3*R*,4*S*,5*R*)-3-(Hydroxymethyl)piperidine-3,4,5-triol (10)

Compound **10** (22 mg, 80% yield) was obtained as a viscous liquid from **43** (75 mg, 0.17 mmol) using the same procedure which was used to obtain **5**. R_f: 0.2 (methanol : ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = +13.04 (c 1.15, CH_3OH), lit.[29b] $[\alpha]_D^{25}$ = +11.0 (c 0.2, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 3.93 (d, 1H, J = 3.92 Hz), 3.68 (d, 1H, J = 4.40 Hz), 3.50 (dd, 2H, J = 11.96, 11.96 Hz), 3.26 (dd, 1H, J = 13.68, 13.44 Hz) 3.18–3.11 (m, 2H), 2.99 (d, 1H, J = 13.10 Hz). ^{13}C NMR (125 MHz, D_2O): δ 71.6, 67.8, 66.5, 63.5, 46.0, 45.2. HRMS (ESI): calcd for $C_6H_{14}NO_4$ $[M + H]^+$ 164.0917; found 164.0925.

(3*S*,4*R*,5*S*)-5-(Hydroxymethyl)piperidine-3,4-diol (11)

Compound **11** (23 mg, 89% yield) was obtained as a viscous liquid from **48** (75 mg, 0.17 mmol) using the same procedure which was used to obtain **5** as a viscous liquid. R_f: 0.2 (ethyl acetate : methanol, 4 : 1), $[\alpha]_D^{28}$ = +2.35 (c 1.5, MeOH), lit.[28] $[\alpha]_D^{25}$ = +3.5 (c 1.02, EtOH). ^{1}H NMR (400 MHz, D_2O): δ 3.91 (br s, 1H, H-4), 3.71–3.69 (m, 1H, H-3), 3.49 (dd, 1H, J = 6.84, 11.20 Hz, H-7), 3.39 (dd, 1H, J = 7.08, 11.20 Hz, H-7′), 3.02–2.94 (m, 2H, H-2, H-6), 2.79 (t, 1H, J = 11.72 Hz, H-6′), 2.63 (t, 1H, J = 12.72 Hz, H-2′), 1.90–1.85 (m, 1H, H-5). ^{13}C NMR (125 MHz, D_2O): δ 66.3, 66.2, 60.1, 42.4, 39.8, 39.6.

HRMS (ESI): calcd for $C_6H_{14}NO_3$ $[M + H]^+$ 148.0968; found 148.0973.

(3*R*,4*S*,5*S*)-3-(Hydroxymethyl)piperidine-3,4,5-triol (12)

Compound **12** (25 mg, 91% yield) was obtained as a viscous liquid from **49** (75 mg, 0.17 mmol) using the same procedure which was used to obtain **5**. R_f: 0.3 (*i*PrOH : H_2O : NH_4OH 7 : 2:1), $[\alpha]_D^{28}$ = +19.23 (*c* 0.65, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 4.02–3.98 (m, 1H, H-3), 3.70 (d, 1H, *J* = 2.75 Hz, H-4), 3.51 (d, 1H, *J* = 12.25 Hz, H-6), 3.42 (d, 1H, *J* = 12.20 Hz, 1H, H-6′), 2.93 (dd, 1H, *J* = 4.90, 11.90 Hz, H-2), 2.78–2.67 (m, 3H, H-7, H-7′, H-2′). ^{13}C NMR (125 MHz, D_2O): δ 73.1, 68.8, 64.1, 64.0, 44.7, 43.0. HRMS (ESI): calcd for $C_6H_{14}NO_4$ $[M + H]^+$ 164.0917; found 164.0922.

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