DOI: 10.1002/ejoc.200801301

Facile Aza-Claisen Rearrangement of Glycals: Application in the Synthesis of 1-Deoxy-L-iminosugars

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Dedicated to Professor Dr. Hans-Ulrich Reißig on the occasion of his 60th birthday

Keywords: Carbohydrates / Iminosugars / Azasugars / Rearrangement / Enzymes / Inhibitors

2-*C*-Methylene-*N*-glycosyl amides have been obtained from 2-(hydroxymethyl)glycals through a facile aza-Claisen rearrangement. This rearrangement has also been utilized in the synthesis of L-*allo*-deoxynojirimycin, a moderate inhibitor of human lysosomal α-mannosidase (IC_{50} = 64 μM), and two new *C*-5-(hydroxymethyl) analogues of L-*altro*-deoxynojirimycin and L-*ido*-deoxynojirimycin.

Introduction

The design and synthesis of glycosidase inhibitors have gained huge momentum in recent years along with developments in the field of glycobiology.[1] Such inhibitors are not only useful as potential drugs for a variety of carbohydrate-mediated diseases, but can also provide interesting insights into the mechanism of enzymatic glycoside hydrolysis.[2] Polyhydroxylated piperidines (commonly known as aza- or iminosugars) are an important class of glycosidase inhibitors[3] with possible therapeutic uses in the treatment of diabetes,[4] cancer,[5] HIV,[6] and other metabolic disorders.[7] Ever since the discovery of 1-deoxynojirimycin (**1**; DNJ), a potent α-glucosidase inhibitor, the synthesis and biological evaluation of naturally occurring as well as synthetic azasugars have received considerable attention.[8] Notable contributions in this area have led to the development of miglitol (**2**; *N*-hydroxyethyl-1-deoxynojirimycin) and miglustat (**3**; *N*-butyl-1-deoxynojirimycin) for use in patients with type II diabetes and type I Gaucher's disease, respectively (Figure 1). In recent years, research efforts have been directed towards the development of general and flexible methodologies for accessing a variety of azasugars through common precursors.[9] With this in mind, we decided to explore the aza-Claisen rearrangement[10] (or Overman rearrangement), which has been widely used in the synthesis of several nitrogen-containing natural products. Very recently, α- and β-*N*-glycosyl amides have been obtained stereoselectively by a palladium-catalyzed aza-Claisen rearrangement of glycals, which were later transformed into glycosyl ureas.[11]

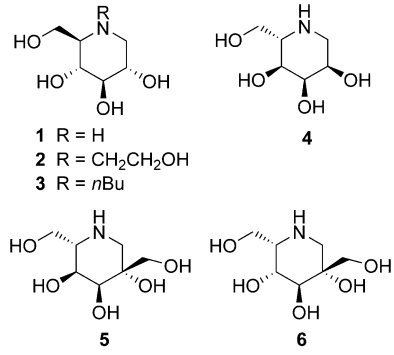

Figure 1. Piperidine-based iminosugars.

Following on from our previous work on glycals and their use in the synthesis of biologically important molecules,[12] we expected that such rearrangements of 2-(hydroxymethyl)glycals would afford *N*-glycosyl amides with an *exo*-methylene unit at C-2. Although Ramesh and Balasubramanian[13] described the introduction of a nitrogen functionality at C-1, they exploited the Mitsunobu reaction employing phthalimide as the nucleophile. We perceived that glycosyl amides obtained by the rearrangement reaction would not only be important in the synthesis of glycopeptides, but they could also provide access to azasugars by suitable manipulations of the carbohydrate scaffold. Thus, we report herein a facile aza-Claisen rearrangement of 2-(hydroxymethyl) glycals and its application to the synthesis of L-*allo*-deoxynojirimycin (**4**) and two new azasugars, namely 5-(hydroxymethyl) analogues of L-*altro*- and L-*ido*-deoxynojirimycin, **5** and **6**, respectively (Figure 1).

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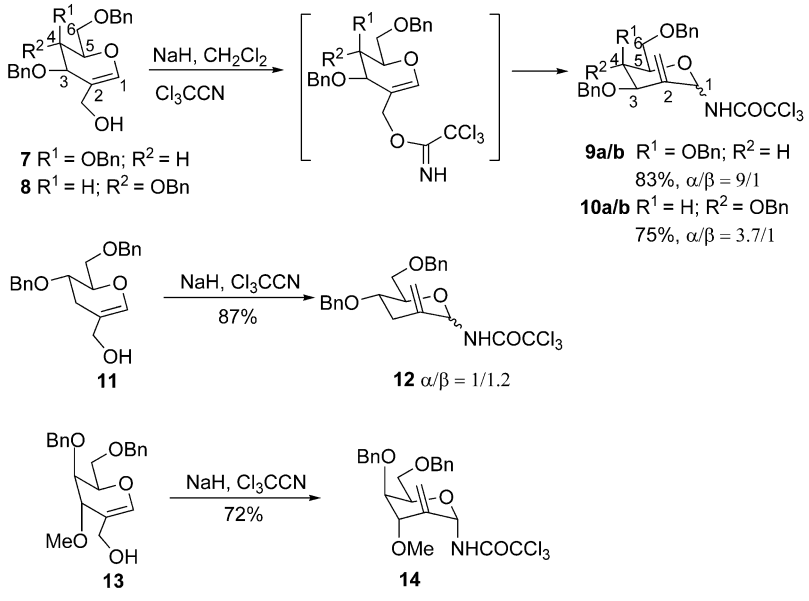
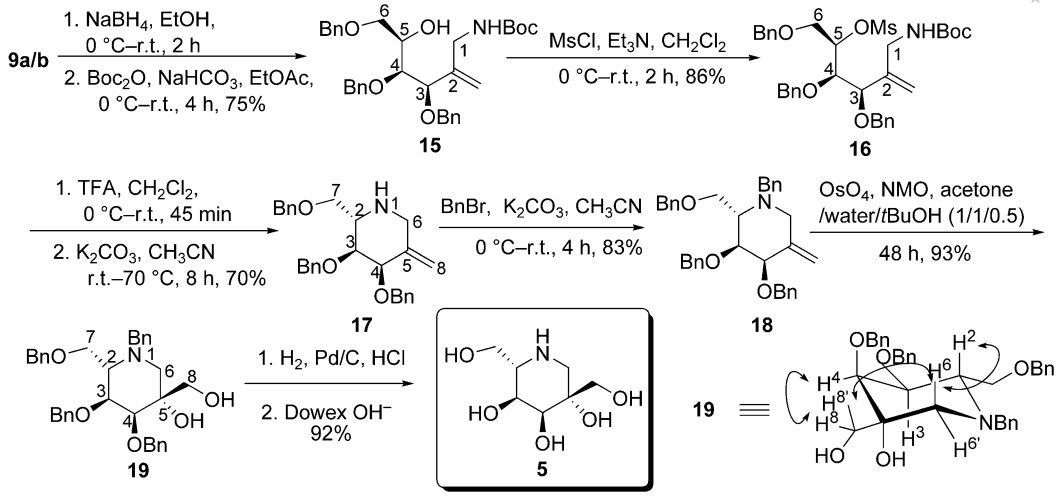
Results and Discussion

The aza-Claisen rearrangement involves the reaction of allylic alcohol with trichloroacetonitrile to give the trichloroacetimidate, which then rearranges to give allylic trichloroacetamide. These rearrangements are either carried out thermally or by Hg^{II} or Pd^{II} catalysis. Thus, when 3,4,6-tri-*O*-benzyl-2-*C*-(hydroxymethyl)galactal (**7**) was subjected to the conditions for imidate preparation using NaH and trichloroacetonitrile, we did not observe the formation of the expected imidate; instead we isolated the rearranged product **9a/b**. Clearly, the formation of the imidate and subsequent rearrangement seems to occur in the same pot without any catalysis or high temperature required. Although such a facile rearrangement is being observed for the first time with pyran glycals, such a rearrangement has been reported previously in the case of furan glycals.[14] Thus, the galactal derivative **7**[15] afforded a separable mixture of α- and β-*N*-glycosyltrichloroacetamidates **9a** and **9b** in a 9:1 ratio. The ^1H and ^{13}C NMR spectra were in complete agreement with their structures. The configuration of **9a** was confirmed by NOE experiments wherein irradiation of the signal of 1-H led to an enhancement of the signal of one of the olefinic protons, whereas no enhancement was seen of the signal of 5-H. Reaction with glucal derivative **8**[15] afforded an inseparable mixture of α- and β-*N*-glycosyltrichloroacetamidates **10a** and **10b** in a 3.7:1 ratio. The minor isomer was isolated as a mixture with the major isomer. However, a pure sample of the major isomer could be obtained by column chromatography. By employing glucal derivative **11**,[16] a 3-deoxy derivative, an inseparable mixture of α/β-trichloroacetamidate **12** was obtained in a 1:1.2 ratio. Clearly the absence of a substituent at C-3 appears to be responsible for the observed low stereoselectivity. With glycal derivative **13**,[17] in which the configuration at the C-3 center is inverted, the α anomer was obtained exclusively (Scheme 1). The structures of all the glycosyl amides were confirmed by 1D and 2D NMR and by NOE experiments (see the Supporting Information for details).

With the glycosyl amides in hand, we focused our attention on their conversion into azasugar intermediates. For this purpose, hydrolysis of the amide followed by ring-opening was required. Attempts to hydrolyze the amides under basic[18a,18b] as well as acidic[18c] conditions gave poor yields of the free amine and therefore deprotection was achieved by using $NaBH_4$.[18d] Thus, reaction of an anomeric mixture of glycosyl amides **9a** and **9b** with $NaBH_4$ in ethanol led to the reduction of the amide followed by ring-opening to provide the corresponding free amine, which was immediately treated with di-*tert*-butyl pyrocarbonate to give the Boc-protected amine **15** in 75% yield. As a stereocenter is lost at this stage, an anomeric mixture of **9a** and **9b** was employed directly without any need for their separation. Mesylation of the amino alcohol **15** proceeded smoothly to afford **16** in good yield (Scheme 2). Removal of the NHBoc group using CF_3COOH in CH_2Cl_2 followed by intramolecular S_N2 cyclization induced by K_2CO_3 gave the cyclized product **17** in 70% yield with an inversion of the stereochemistry at C-2.[19] A coupling constant value of $J_{2,3}$ = 10.0 Hz was observed in its ^1H NMR spectrum, which indicates a *trans* diaxial orientation of 2-H and 3-H, thus supporting the existence of a $^1C_4$ conformation. It is expected that synthon **17** can be easily converted into various targets by suitably functionalizing the exocyclic double bond.[9d,20] Protection of the secondary amine as an *N*-benzyl derivative gave **18**. Dihydroxylation using catalytic osmium tetroxide and NMO afforded **19** as a single diastereomer. In the ^1H NMR spectrum of **19**, the signal for 3-H appears as a doublet of doublets with coupling constants of $J_{2,3}$ = 9.4 Hz and $J_{3,4}$ = 2.9 Hz. This indicates a *trans* diaxial orientation of 2-H and 3-H and the existence of a $^1C_4$ conformation in **19**. The stereochemistry at the newly generated quaternary center



Scheme 1. One-pot rearrangement of the 2-hydroxyglycals.



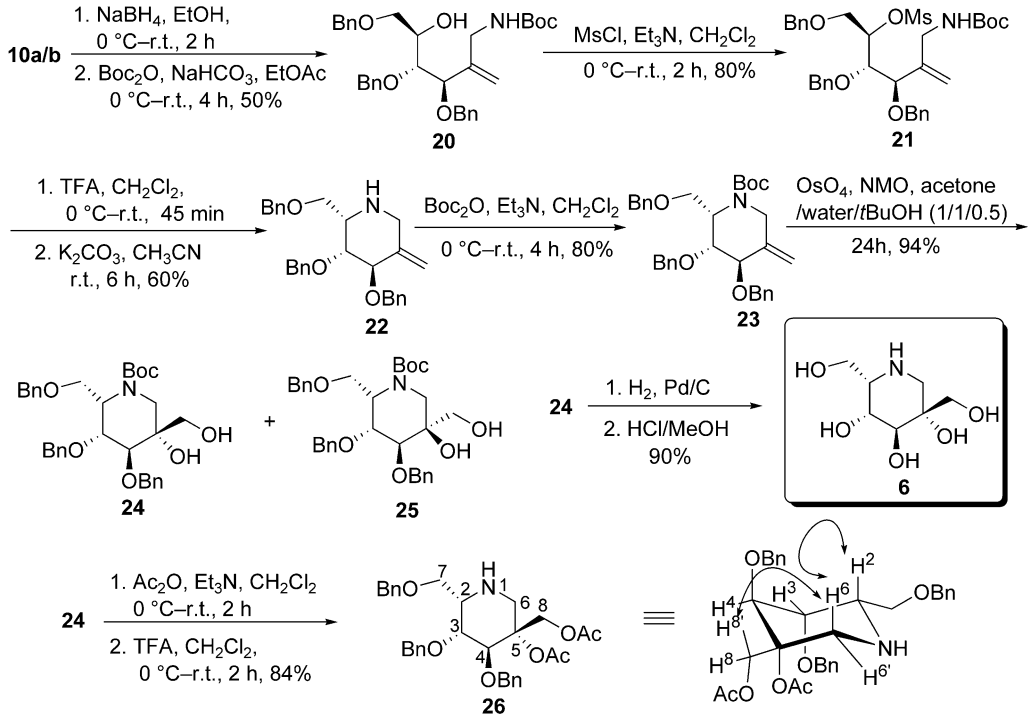
Scheme 2. Synthesis of iminosugar **5**.

C-5 was adjudged on the basis of NOE experiments (Scheme 2). Irradiation of the signal of one of the CH_2 hydrogen atoms attached to the quaternary center, that is, 8-H, led to an enhancement of the signal of the 4-H proton, whereas irradiation of the signal of the other CH_2 hydrogen, that is, 8′-H, led to an enhancement of the signal of the axial hydrogen at C-6. No enhancement of the signal of 3-H was observed when 8-H and 8′-H were irradiated. These correlations support the stereochemical outcome of **19** with the dihydroxylation occurring only from the less hindered side of the double bond with the hydroxy group occupying an α orientation (axial) and the hydroxymethyl group a β orientation (equatorial) in the obtained diol. Hydrogenolysis of **19** with 10% Pd/C and H_2 in ethanol containing hydrochloric acid gave the deprotected compound, which afforded the deprotected *C*-5-(hydroxymethyl)-L-*altro*-DNJ (**5**) after passing through a basic Dowex column. Compound **5** was characterized by spectroscopy.

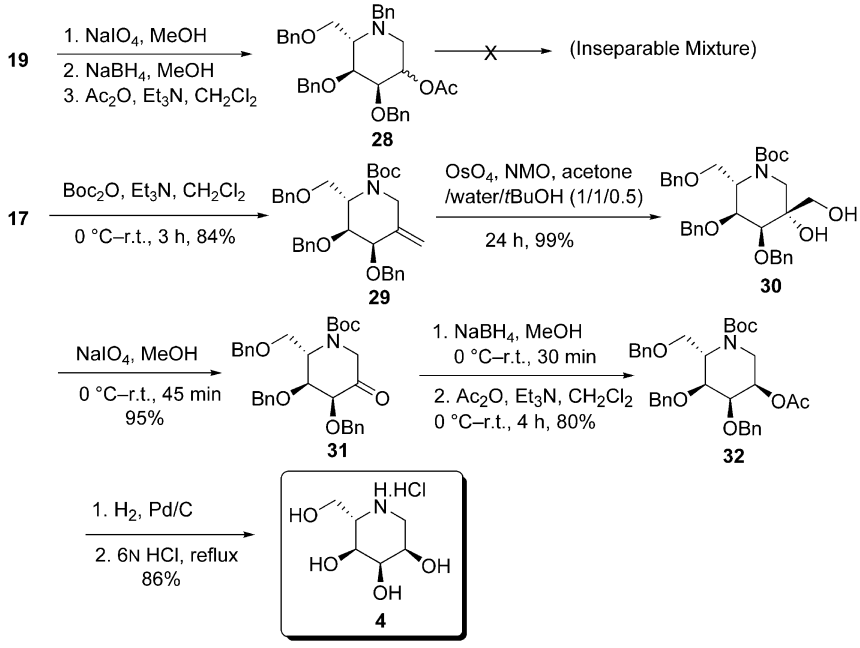
Similarly, glycosyl amides **10a** and **10b** were transformed into 5-(hydroxymethyl)-L-*ido*-DNJ (**6**; Scheme 3). Reaction of the anomeric mixture of **10a** and **10b** with $NaBH_4$ in ethanol afforded the ring-opened free amine, which on NHBoc protection furnished **20** in 50% yield. Mesylation of this amino alcohol gave **21**, which on NHBoc deprotection followed by cyclization provided the expected product **22**. The appearance in its ^1H NMR spectrum of a doublet at δ = 3.95 ppm for 4-H with a small coupling constant of $J_{3,4}$ = 3.1 Hz indicates the diequatorial disposition of the 3-H and 4-H protons, thus confirming the $^1C_4$ conformation of **22**. Protection of the amine with a benzyl group followed by dihydroxylation afforded an inseparable mixture of diastereomeric diols. Hence we changed the protecting group and instead of benzyl protection, Boc protection of the amine in **22** gave **23**, which on dihydroxylation gave a separable mixture of diastereomeric diols **24** and **25** in a 3:1 ratio. However, because of the presence of rotamers the determination of the exact stereochemistry was difficult at this stage. Thus, acetylation of the major diol **24** followed by removal of the NHBoc protection gave compound **26** the spectroscopic data of which, including COSY and NOE data, permitted the assignment of the stereochemistry at the newly generated stereocenter. The major isomer **24** was finally deprotected in two steps, namely, hydrogenolysis of the benzyl groups using catalytic Pd/C and H_2 and NHBoc deprotection under acidic conditions, to give the deprotected compound **6** in 90% yield.

It has been recently reported that L-*allo*-deoxynojirimycin (**4**; L-*allo*-DNJ) is a moderate inhibitor of human lysosomal α-mannosidase with an IC_{50} value of 64 μM.[21] However, very few syntheses of this azasugar have been reported in the literature.[9b,21,22] We realized that **19** could be an ideal precursor for the synthesis of this molecule. Thus, for the synthesis of L-allo-DNJ, the diol in compound **19** (Scheme 4) was cleaved with sodium periodate to afford the corresponding ketone, which was rather unstable and hence immediately subjected to sodium borohydride reduction. Direct acetylation of the crude product afforded **28** as an inseparable mixture in an 80:20 diastereomeric ratio. This failure forced us to revert back to synthon **17**, which on Boc protection instead of benzyl protection gave compound **29**. Dihydroxylation with OsO_4/NMO afforded the diol **30**. Sodium periodate oxidation of **30** gave the desired ketone **31**, which was reduced with sodium borohydride. Acetylation of the crude product gave **32** as a separable mixture in a 90:10 diastereomeric ratio. The stereochemistry of the newly generated hydroxy group was confirmed by COSY and NOE experiments (see the Supporting Information). Finally, deprotection of the benzyl groups under catalytic Pd/C-H_2, followed by treatment with 6 N aq. HCl allowed the removal of the acetate and NHBoc protecting groups to provide L-*allo*-deoxynojirimycin (**4**), which was characterized as its hydrochloride salt. The spectral data of **4** were in complete agreement with those reported in the literature.[9b]

The azasugar inhibitory activities of analogues **5** and **6** towards a few commercially available glycosidases were evaluated at millimolar concentrations (Table 1). The parent L-*altro*-DNJ is known to inhibit α-glucosidase (rice) at



Scheme 3. Synthesis of iminosugar **6**.



Scheme 4. Synthesis of iminosugar **4**.

a concentration of 0.45 mM (IC_{50}).[21] Its hydroxymethyl analogue **5** not only showed inhibition against α-glucosidase, but also showed inhibition towards α-galactosidase (coffee beans) and moderate inhibition towards β-galactosidase (bovine liver; entries 1, 3, and 4). Similarly, the hydroxymethyl analogue **6** showed selective inhibition against α-galactosidase (coffee beans; entry 3), although its parent azasugar L-*ido*-DNJ is not known to inhibit any of the studied enzymes.[21] These studies indicate that although **5** showed inhibition against various glycosidases, **6** is not only selective, but a better inhibitor than the parent compound. It further suggests that structural variations of these molecules could further promote glycosidase inhibition.

Table 1. IC_{50} values for compounds **5** and **6**.[a]

Entry	Enzyme	IC_{50}[b] [mM]	
		5	**6**
1	α-glucosidase (rice)	1.0	NI
2	β-glucosidase (almonds)	NI	NI
3	α-galactosidase (coffee beans)	29	8.5
4	β-galactosidase (bovine liver)	0.76	NI

[a] Inhibition studies were carried out at millimolar concentrations, the optimal pH of the enzymes and 37 °C. [b] NI = no inhibition at <1.0 mM concentration of the inhibitor.

Conclusions

We have developed a new route to L-azasugars and their analogues by the aza-Claisen rearrangement of glycals. The new azasugar analogue **6** proved to be a more potent inhibitor than the parent sugar. Further variations of these molecules and their inhibitory studies can provide new insights into the inhibitory activities of L-azasugars.

Experimental Section

General: Infrared spectra were recorded with a Bruker FT/IR Vector 22 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a JEOL LA-400 (400 and 100 MHz, respectively) 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 with a Waters HAB 213 Q Tof Premier Micromass or Micromass Quattro II triple Quadrupole Mass spectrometer. Optical rotations were recorded with an Autopol II automatic polarimeter at the wavelength of the sodium D line (589 nm) at 25 °C. Elemental analyses were carried out with a Thermoquest CE-instruments EA-1110 CHNS analyzer. 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 precoated on aluminium plates. Melting points were determined with a Fischer-John melting point apparatus and are uncorrected. All solvents and common reagents were purified by established procedures.

General Procedure for the Synthesis of *N*-Glycosyltrichloroacetamides: A solution of glycal (0.22 mmol, 1 equiv.) in dichloromethane (2 mL) was cooled to 0 °C. Trichloroacetonitrile (0.33 mmol, 1.5 equiv.) was added to it, followed by the addition of NaH (0.26 mmol, 1.2 equiv.) in small portions. The resulting mixture was stirred at 0 °C for 30 min. Then the cooling bath was removed and stirring was continued for a period of time, as indicated by TLC analysis. The reaction was quenched by adding a saturated NH_4Cl solution. The reaction mixture was then extracted with dichloromethane (2 × 20 mL), the combined organic extracts were washed with water and brine solution, dried with sodium sulfate, filtered, and concentrated. Column chromatography of the crude reaction mixture afforded the *N*-glycosyltrichloroacetamides.

***N*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methylene-α-D-*lyxo*-hexopyranosyl)trichloroacetamide (9a):** Compound **9a** (99 mg, 74.8% yield) was obtained as a colorless solid from glycal **7** (100 mg, 0.22 mmol) by following the general procedure described above over 6 h. R_f = 0.4 (hexane/ethyl acetate, 9:1); m.p. 90 °C. $[\alpha]_D^{25}$ = +37.0 (*c* = 2.1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3334, 1725, 1664 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.20 (m, 16 H, Ar*H*, N*H*$COCl_3$), 5.99 (d, *J* = 7.0 Hz, 1 H, 1-H), 5.45 (s, 1 H, olefinic), 5.35 (s, 1 H, olefinic), 4.79 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 4.64–4.53 (m, 3 H, OCH_2Ph), 4.46 (d, *J* = 11.9 Hz, 1 H, OCH_2Ph), 4.40 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.20 (br. s, 1 H, 3-H), 4.09 (dt, *J* = 2.4, 6.1 Hz, 1 H, 5-H), 3.95 (t, *J* = 2.4 Hz, 1 H, 4-H), 3.71 (dd, *J* = 6.3, 10.2 Hz, 1 H, 6′-H), *3*.67 (dd, *J* = 6.3, 10.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 138.9, 138.3, 138.0, 137.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 114.7, 92.5, 79.7, 74.8, 74.1, 73.5, 73.5, 73.4, 71.2, 68.1 ppm. HRMS (ESI): calcd. for $C_{30}H_{30}Cl_3NO_5$ $[M - H]^-$ 588.1112; found 588.1110.

***N*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methylene-β-D-*lyxo*-hexopyranosyl)trichloroacetamide (9b):** Compound **9b** (11 mg, 8.31% yield) was obtained as a colorless liquid from glycal **7** (100 mg, 0.22 mmol) by following the general procedure described above over 6 h. R_f = 0.4 (hexane/ethyl acetate, 9:1). $[\alpha]_D^{25}$ = –42.6 (*c* = 2.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3335, 1721, 1662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 6.8 Hz, 1 H, N*H*$COCl_3$), 7.37–7.23 (m, 15 H, Ar*H*), 5.69 (d, *J* = 8.2 Hz, 1 H, 1-H), 5.55 (s, 1 H, olefinic), 5.27 (s, 1 H, olefinic), 4.90 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.70–4.61 (m, 3 H, OCH_2Ph), 4.47 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.42 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.13 (br. s, 1 H, 3-H), 4.03 (br. s, 1 H, 5-H), 3.88 (m, 1 H, 4-H), 3.57 (m, 2 H, 6-H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 140.2, 138.0, 137.8, 137.7, 128.5, 128.3, 128.2, 127.8, 127.5, 110.0, 92.6, 79.7, 79.2, 75.9, 74.4, 74.1, 73.5, 71.8, 68.6 ppm. HRMS (ESI): calcd. for $C_{30}H_{30}Cl_3NO_5$ $[M - H]^-$ 588.1112; found 588.1111.

***N*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methylene-α-D-*arabino*-hexopyranosyl)trichloroacetamide (10a):** Compound **10a/b** (100 mg, 75.5% yield) was obtained as a 3.7:1 mixture of α and β anomers, respectively, from glycal **8** (100 mg, 0.22 mmol) by following the general procedure described above over 10 h. The pure sample of α anomer **10a** was obtained as a colorless solid by column chromatography. R_f = 0.4 (hexane/ethyl acetate, 9:1); m.p. 64 °C. $[\alpha]_D^{25}$ = +43.1 (*c* = 1.6, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3337, 1722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 16 H, Ar*H*, N*H*$COCCl_3$), 6.06 (d, *J* = 7.5 Hz, 1 H, 1-H), 5.43 (s, 1 H, olefinic), 5.41 (s, 1 H, olefinic), 4.75–4.66 (m, 2 H, OCH_2Ph), 4.60–4.47 (m, 4 H, OCH_2Ph), 4.14 (d, *J* = 5.6 Hz, 1 H, 3-H), 3.87–3.85 (m, 1 H, 5-H), 3.77–3.73 (m, 2 H, 6′-H, 4-H), 3.68 (dd, *J* = 3.6, 10.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 139.6, 138.0, 137.6, 137.5, 128.4, 128.3, 128.0, 127.8, 127.6, 116.6, 92.4, 79.3, 79.1, 78.2, 74.1, 73.6, 73.5, 71.9, 69.1 ppm. HRMS (ESI): calcd. for $C_{30}H_{30}Cl_3NO_5$ $[M + H]^+$ 588.1112; found 588.1115.

***N*-(4,6-Di-*O*-benzyl-2,3-dideoxy-2-*C*-methylene-α/β-D-*threo*-hexopyranosyl)trichloroacetamide (12a/b):** Compound **12a/b** (124 mg, 87% yield) was obtained as a 1:1.2 mixture of α and β anomers, respectively, from glycal **11** (100 mg, 0.29 mmol) by following the general procedure described above over 6 h. R_f = 0.4 (hexane/ethyl acetate, 9:1). Colorless liquid. $[\alpha]_D^{25}$ = –20.0 (*c* = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3373, 1726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, mixture of anomers): δ = 7.95 (d, *J* = 8.5 Hz, 1 H, N*H*$COCl_3$, α anomer), 7.35–7.22 (m, 21 H, Ar*H*, both α and β anomers, N*H*$COCl_3$, β anomer), 6.02 (d, *J* = 8.5 Hz, 1 H, 1-H, α anomer), 5.65 (d, *J* = 9.2 Hz, 1 H, 1-H, β anomer), 5.15 (s, 1 H, olefinic, α anomer), 5.13 (s, 1 H, olefinic, α anomer), 5.00 (s, 2 H, olefinic, β anomer), 4.65–4.42 (m, 8 H, OCH_2Ph, both α and β anomers), 3.98 (dd, *J* = 4.16, 8.32 Hz, 1 H, 5-H, α anomer), 3.89 (m, 1 H, 4-H, α anomer), 3.77–3.72 (m, 4 H, 4-H, 5-H, 6-H, 6′-H, β anomer), 3.67 (dd, *J* = 4.6, 10.4 Hz, 1 H, 6′-H, α anomer), 3.57 (dd, *J* = 4.8, 10.4 Hz, 1 H, 6-H, α anomer), 2.98 (dd, *J* = 4.6, 13.6 Hz, 1 H, 3′-H, β anomer), 2.69 (br. d, *J* = 11.7 Hz, 1 H, 3′-H, α anomer), 2.62 (dd, *J* = 5.1, 11.7 Hz, 1 H, 3-H, α anomer), 2.35 (br. t, *J* = 12.4 Hz, 1 H, 3-H, β anomer) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of ano-

mers): δ = 161.3, 161.1, 140.3, 137.9, 137.3, 128.4, 128.1, 127.7, 114.7, 110.4, 92.5, 92.3, 80.0, 79.7, 78.3, 73.8, 73.6, 73.1, 71.3, 70.9, 69.8, 68.7, 37.1, 31.7 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}Cl_3NO_4$ $[M + H]^+$ 484.0849; found 484.0847.

***N*-(4,6-Di-*O*-benzyl-3-*O*-methyl-2-deoxy-2-*C*-methylene-α/β-D-*xylo*-hexopyranosyl)trichloroacetamide (14):** Compound **14** (99 mg, 71.2% yield) was obtained as a viscous liquid from glycal **13** (100 mg, 0.27 mmol) by following the general procedure described above over 8 h. R_f = 0.5 (hexane/ethyl acetate, 9:1). $[\alpha]_D^{25}$ = +32.8 (*c* = 1.3, CH_2Cl_2). IR (neat): ṽ = 3373, 1726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.5 Hz, 1 H, N*H*$COCl_3$), 7.27–7.18 (m, 10 H, Ar*H*), 5.83 (d, *J* = 8.5 Hz, 1 H, 1-H), 5.39 (s, 1 H, olefinic), 5.13 (s, 1 H, olefinic), 4.51 (s, 2 H, OCH_2Ph), 4.47 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.38 (d, *J* = 11.7 Hz, 1 H, OCH_2Ph), 4.21 (t, *J* = 6.3 Hz, 1 H, 5-H), 3.69 (d, *J* = 2.9 Hz, 1 H, 4-H), 3.61–3.55 (m, 2 H, 6′-H, 3-H), 3.53 (dd, *J* = 9.5, 5.6 Hz, 1 H, 6-H), 3.24 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 138.0, 137.7, 135.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 119.8, 93.2, 79.8, 79.4, 74.3, 73.5, 73.0, 68.4, 67.1, 56.7 ppm. HRMS (ESI): calcd. for $C_{24}H_{26}Cl_3NO_5$ $[M + H]^+$ 514.0955; found 514.0957.

***tert*-Butyl (3*R*,4*S*,5*R*)-3,4,6-Tris(benzyloxy)-5-hydroxy-2-methylenehexylcarbamate (15):** $NaBH_4$ (258 mg, 0.68 mmol) was added portionwise to a stirred solution of compound **9a**/**b** (100 mg, 0.17 mmol) in dry ethanol (2 mL) at 0 °C. The reaction mixture was stirred for 2 h and then quenched by the addition of a saturated NH_4Cl solution (2 mL). Ethanol was removed in vacuo and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water, brine, dried with Na_2SO_4, and the solvent was removed to obtain the crude amino alcohol, which was submitted to subsequent reaction without any further purification. Thus, the amino alcohol was taken in ethyl acetate (2 mL) and cooled to 0 °C. Then a saturated $NaHCO_3$ solution (2 mL) was added followed by Boc_2O (0.04 mL, 0.19 mmol) and the reaction mixture was stirred for 4 h. Then it was extracted with ethyl acetate, washed with water and brine, and dried with Na_2SO_4. Solvent evaporation followed by purification by column chromatography gave compound **15** (0.070 g, 75.5%) as a viscous liquid. R_f = 0.5 (hexane/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = –20.9 (*c* = 1.9, CH_2Cl_2). IR (neat): ṽ = 3361, 3031, 1713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 15 H, Ar*H*), 5.28 (s, 1 H, olefinic), 5.27 (s, 1 H, olefinic), 4.72 (br. s, 1 H, N*H*Boc), 4.60–4.53 (m, 5 H, OCH_2Ph), 4.30 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.11–4.07 (m, 2 H, 3-H, 5-H), 3.76 (m, 2 H, 1-H, 1′-H), 3.66 (m, 1 H, 4-H), 3.51–3.48 (m, 2 H, 6-H, 6′-H), 2.79 (br. s, 1 H, O*H*), 1.43 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 143.7, 138.1, 137.9, 137.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.1, 115.5, 80.7, 79.2, 74.1, 73.4, 71.2, 70.9, 69.6, 42.7, 28.4 ppm. HRMS (ESI): calcd. for $C_{33}H_{41}NO_6$ $[M + H]^+$ 548.3012; found 548.3012.

***tert*-Butyl (3*R*,4*R*,5*R*)-3,4,6-Tris(benzyloxy)-5-(methylsulfonyloxy)-2-methylenehexylcarbamate (16):** Et_3N (54.6 mg, 0.08 mL, 0.54 mmol) was added to a solution of the amino alcohol **15** (150 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) cooled to 0 °C. Then methanesulfonyl chloride (47 mg, 0.03 mL, 0.41 mmol) was added dropwise to the reaction mixture. A catalytic amount of 4-(dimethylamino)pyridine was also added. The reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with water and brine, and dried with anhydrous Na_2SO_4. Solvent removal followed by column chromatography afforded the mesylated compound **16** (148 mg, 86.5% yield) as a colorless liquid. R_f = 0.6 (hexane/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = +5.64 (*c* = 3.0, CH_2Cl_2). IR (neat): ṽ = 3419, 3031, 1713, 1392 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 15 H, Ar*H*), 5.33 (s, 1 H, olefinic), 5.28 (s, 1 H, olefinic), 5.14 (m, 1 H, 5-H), 4.83 (br. s, 1 H, N*H*Boc), 4.65 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.51–4.39 (m, 5 H, OCH_2Ph), 4.07 (d, *J* = 7.6 Hz, 1 H, 3-H), 3.81–3.75 (m, 3 H, 1-H, 1′-H, 4-H), 3.74 (dd, *J* = 10.7, 7.0 Hz, 1 H, 6′-H), 3.54 (dd, *J* = 10.7, 4.1 Hz, 1 H, 6-H), 2.95 (s, 3 H, SO_2CH_3), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 143.2, 137.8, 137.5, 137.3, 128.4, 128.3, 127.9, 127.7, 116.5, 80.3, 80.1, 79.2, 78.8, 74.9, 73.3, 70.7, 69.4, 42.4, 38.6, 28.4 ppm. HRMS (ESI): calcd. for $C_{34}H_{43}NO_8S$ $[M + H]^+$ 626.2787; found 626.2781.

(2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-methylenepiperidine (17): Trifluoroacetic acid (1.5 mL) was added dropwise to a solution of the mesylate **16** (500 mg, 0.80 mmol) in CH_2Cl_2 (6 mL) at 0 °C over 5 min while stirring. The reaction mixture was then stirred at room temperature for 45 min. Upon cooling the reaction mixture to 0 °C again and diluting with CH_2Cl_2 (5 mL), a 2 M K_2CO_3 solution (10 mL) was added carefully. This mixture was partitioned and the aqueous phase was extracted with DCM (15 × 3 mL). The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, and the solvents removed. The residue was dissolved in CH_3CN (30 mL) and K_2CO_3 (553 mg, 4 mmol) was added. After stirring for 4 h at room temperature, the reaction mixture was heated up to 70 °C and stirred for a further 4 h. The reaction mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residue was extracted with ethyl acetate (3 × 15 mL), washed with water and brine, and dried with Na_2SO_4. Solvent evaporation followed by purification by column chromatography gave compound **17** (242 mg, 70.5% yield) as a viscous liquid. R_f = 0.4 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = –40.9 (*c* = 1.4, CH_2Cl_2). IR (neat): ṽ = 3318, 2864, 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 15 H, Ar*H*), 5.02 (s, 1 H, olefinic), 4.85 (s, 1 H, olefinic), 4.64 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 4.51–4.42 (m, 3 H, OCH_2Ph), 4.34–4.30 (m, 2 H, OCH_2Ph), 4.15 (d, *J* = 2.9 Hz, 1 H, 4-H), 3.76 (dd, *J* = 9.0, 4.1 Hz, 1 H, 7-H), 3.66 (dd, *J* = 9.0, 2.6 Hz, 1 H, 7′-H), 3.49 (d, *J* = 13.6 Hz, 1 H, 6′-H), 3.43 (dd, *J* = 10.0, 2.9 Hz, 1 H, 3-H), 3.33 (m, 1 H, 2-H), 3.21 (d, *J* = 13.6 Hz, 1 H, 6-H), 2.01 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 138.3, 128.3, 128.2, 127.9, 127.7, 127.6, 127.4, 113.0, 79.0, 76.5, 73.4, 70.5, 70.3, 69.0, 54.5, 47.5 ppm. HRMS (ESI): calcd. for $C_{28}H_{31}NO_3$ $[M + H]^+$ 430.2382; found 430.2382.

(2*S*,3*S*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-methylenepiperidine (18): Compound **17** (250 mg, 0.58 mmol) was dissolved in CH_3CN (5 mL) and cooled to 0 °C. K_2CO_3 (161 mg, 1.16 mmol) was added to the reaction mixture followed by BnBr (109 mg, 0.08 mL, 0.64 mmol). After stirring for 4 h at room temperature, the reaction mixture was filtered, the solvent was evaporated, and purification by column chromatography gave the title compound **18** (251 g, 83.0% yield) as a colorless liquid. R_f = 0.6 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{25}$ = –10.8 (*c* = 0.9, CH_2Cl_2). IR (neat): ṽ = 2922, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.27 (m, 20 H, Ar*H*), 4.92 (s, 1 H, olefinic), 4.90 (s, 1 H, olefinic), 4.53 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 4.43 (m, 3 H, OCH_2Ph), 4.29 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.23 (d, *J* = 12.7 Hz, 1 H, OCH_2Ph), 4.02 (d, *J* = 3.2 Hz, 1 H, 4-H), 3.88 (d, *J* = 13.4 Hz, 1 H, NCH_2Ph), 3.79 (dd, *J* = 10.4, 2.9 Hz, 1 H, 7′-H), 3.74 (dd, *J* = 10.4, 4.4 Hz, 1 H, 7-H), 3.61 (dd, *J* = 9.2, 3.2 Hz, 1 H, 3-H), 3.50 (d, *J* = 13.4 Hz, 1 H, NCH_2Ph), 3.17–3.13 (m, 1 H, 2-H), 3.02 (d, *J* = 12.6 Hz, 1 H, 6′-H), 2.93 (d, *J* = 12.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 139.4, 138.4

(2 peaks), 129.1, 128.2, 127.9, 127.8, 127.4, 126.7, 114.7, 76.6, 76.0, 73.3, 71.0, 68.9, 68.0, 60.1, 55.7, 52.8 ppm. HRMS (ESI): calcd. for $C_{35}H_{37}NO_3$ [M + H]$^+$ 520.2851; found 520.2855.

(2*S*,3*S*,4*S*,5*R*)-1-Benzyl-2-(benzyloxymethyl)-3,4-bis(benzyloxy)-5-(hydroxymethyl)piperidin-5-ol (19): NMO (66 mg, 0.56 mmol) and OsO_4 (25 mg/mL solution in *t*BuOH, 0.02 mL, 0.002 mmol) were added to a stirred solution of compound **18** (250 mg, 0.48 mmol) in acetone/water/*t*BuOH (5 mL, 1:1:0.5) at room temperature. The reaction mixture was stirred for 48 h and then it was treated with $Na_2S_2O_5$ (106 mg, 0.56 mmol). The reaction mixture was stirred for a further 30 min and then 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 by column chromatography gave the compound **19** (198 mg, 74.4% yield, based on starting material recovered 93.0% yield) as a viscous liquid along with the recovered starting material (50 mg, 20.0% yield). R_f = 0.5 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = +11.6 (*c* = 1.8, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3436, 2921, 1096 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 20 H, Ar*H*), 4.83 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.69 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.51 (m, 2 H, OCH_2Ph), 4.43 (s, 2 H, OCH_2Ph), 4.18 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 3.98 (dd, *J* = 9.4, 2.9 Hz, 1 H, 3-H), 3.86 (d, *J* = 2.9 Hz, 1 H, 4-H), 3.80–3.77 (m, 2 H, 7-H, 7′-H), 3.57 (d, *J* = 10.4 Hz, 1 H, 8′-H), 3.40 (d, *J* = 11.2 Hz, 1 H, 8-H), 3.27 (d, *J* = 13.2 Hz, 1 H, NCH_2Ph), 2.86 (br. d, *J* = 9.2 Hz, 1 H, 2-H), 2.49 (d, *J* = 11.7 Hz, 1 H, 6-H), 2.44 (d, *J* = 11.7 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 138.7, 138.2, 138.1, 128.8, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.0, 76.1, 74.3, 73.2, 72.3, 72.2, 66.4, 65.6, 61.5, 56.8, 53.2 ppm. HRMS (ESI): calcd. for $C_{35}H_{39}NO_5$ [M + H]$^+$ 554.2906; found 554.2903.

(2*S*,3*S*,4*S*,5*R*)-2,5-Bis(hydroxymethyl)piperidine-3,4,5-triol (5): A solution of **19** (100 mg, 0.18 mmol) in ethanol (5 mL) containing conc. HCl (0.04 mL) was stirred under H_2 in the presence of 10% Pd/C (50 mg) for 3 d. After completion of the reaction, the mixture was filtered through a Celite pad, the filtrate was concentrated, and the residue was passed through a Dowex (50X) basic resin column and concentrated under reduced pressure to give the iminosugar **5** (32 mg, 91.7% yield) as a viscous liquid. R_f = 0.3 (ethyl acetate/methanol, 4:1). $[\alpha]_D^{25}$ = –9.68 (*c* = 0.6, MeOH). ^{1}H NMR (400 MHz, D_2O): δ = 3.93 (br. d, *J* = 10.72 Hz, 1 H), 3.87–3.81 (m, 1 H), 3.73–3.66 (m, 2 H), 3.53 (d, *J* = 12.9 Hz, 1 H), 3.45 (d, *J* = 12.9 Hz, 1 H), 3.19–3.11 (m, 1 H), 3.02 (d, *J* = 13.2 Hz, 1 H), 2.97 (d, *J* = 13.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 72.5, 68.5, 64.0, 63.6, 58.2, 55.6, 44.5 ppm. HRMS (ESI): calcd. for $C_7H_{15}NO_5$ [M + H]$^+$ 194.1028; found 194.1026.

***tert*-Butyl (3*R*,4*R*,5*R*)-3,4,6-Tris(benzyloxy)-5-hydroxy-2-methylenehexylcarbamate (20):** Compound **20** (46 mg, 50% yield) was obtained from **10a/b** (100 mg, 0.17 mmol) by following the same procedure as that used to obtain **15**. R_f = 0.5 (hexane/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = +14.7 (*c* = 1.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3427, 2922, 1713, 1093 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 15 H, Ar*H*), 5.24 (s, 1 H, olefinic), 5.23 (s, 1 H, olefinic), 4.70 (br. s, 1 H, N*H*Boc), 4.63–4.50 (m, 5 H, OCH_2Ph), 4.30 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.10 (d, *J* = 3.8 Hz, 1 H, 3-H), 3.94 (br. s, 1 H, 5-H), 3.74 (m, 2 H, 1-H, 1′-H), 3.66 (m, 1 H, 4-H), 3.59 (m, 2 H, 6-H, 6′-H), 2.67 (br. s, 1 H, O*H*), 1.44 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 143.4, 138.2, 138.0, 137.8, 128.3, 128.2, 127.9, 127.8, 127.7, 114.5, 81.0, 80.7, 79.3, 74.5, 73.4, 71.2, 71.0, 70.4, 42.7, 28.4 ppm. HRMS (ESI): calcd. for $C_{33}H_{41}NO_6$ [M + H]$^+$ 548.3012; found 548.3010.

***tert*-Butyl (3*R*,4*S*,5*R*)-3,4,6-Tris(benzyloxy)-5-methylsulfonyloxy-2-methylenehexylcarbamate (21):** Compound **21** (91 mg, 79.8% yield) was obtained from **20** (100 mg, 0.18 mmol) using the procedure that was used to obtain **16**. R_f = 0.6 (hexane/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = +15.8 (*c* = 1.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3424, 3031, 1712, 1392 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 15 H, Ar*H*), 5.25 (s, 1 H, olefinic), 5.11 (s, 1 H, olefinic), 4.90 (br. s, 1 H, 5-H), 4.80 (br. s, 1 H, N*H*Boc), 4.75 (br. s, 2 H, OCH_2Ph), 4.56–4.45 (m, 3 H, OCH_2Ph), 4.32 (d, *J* = 11.4 Hz, 1 H, OCH_2Ph), 4.05 (br. s, 1 H), 3.95 (br. d, *J* = 6.6 Hz, 1 H, 3-H), 3.82–3.72 (m, 4 H), 2.98 (s, 3 H, SO_2CH_3), 1.45 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 142.9, 138.0, 137.8, 137.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 115.7, 82.7, 82.5, 81.5, 79.3, 75.5, 73.2, 71.0, 68.3, 41.5, 38.2, 28.4 ppm. HRMS (ESI): calcd. for $C_{34}H_{43}NO_8S$ [M + H]$^+$ 626.2787; found 626.2784.

(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-methylenepiperidine (22): Compound **22** (82 mg, 59.8% yield) was obtained from **21** (200 mg, 0.32 mmol) using the procedure that was used to obtain **17**. R_f = 0.4 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = +26.5 (*c* = 0.7, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3317, 2866, 1457 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 15 H, Ar*H*), 5.14 (s, 1 H, olefinic), 4.94 (s, 1 H, olefinic), 4.57–4.52 (m, 3 H, OCH_2Ph), 4.45–4.42 (m, 2 H, OCH_2Ph), 4.26 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 3.95 (d, *J* = 3.1 Hz, 1 H, 4-H), 3.68 (dd, *J* = 3.1, 1.1 Hz, 1 H, 3-H), 3.52 (d, *J* = 13.4 Hz, 1 H, 6′-H), 3.49 (dd, *J* = 8.0, 6.3, Hz, 1 H, 7′-H), 3.45–3.38 (m, 2 H, 2-H, 7-H), 3.32 (d, *J* = 13.7 Hz, 1 H, 6-H), 1.9 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.2, 138.2, 128.1, 127.7, 127.4, 115.1, 77.1, 76.5, 73.2, 72.0, 70.5, 69.2, 54.2, 48.2 ppm. HRMS (ESI): calcd. for $C_{28}H_{31}NO_3$ [M + H]$^+$ 430.2382; found 430.2385.

***tert*-Butyl (2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-methylenepiperidine-1-carboxylate (23):** Compound **22** (100 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Et_3N (25 mg, 0.04 mL, 0.25 mmol) was added followed by Boc_2O (55 mg, 0.06 mL, 0.25 mmol) and the reaction mixture was stirred for 4 h. It was then extracted with CH_2Cl_2 (3 × 10 mL), washed with water and brine, and dried with Na_2SO_4. Solvent evaporation followed by purification by column chromatography gave compound **23** (99 mg, 80.4% yield) as a viscous liquid. R_f = 0.6 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{25}$ = +18.5 (*c* = 0.8, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2925, 1694, 1110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 15 H, Ar*H*), 5.21 (s, 1 H, olefinic), 5.04 (s, 1 H, olefinic), 4.72–4.64 (m, 5 H), 4.57 (br. d, *J* = 11.9 Hz, 1 H), 4.46 (d, *J* = 12.2 Hz, 1 H), 4.28 (br. d, *J* = 8.7 Hz, 1 H), 3.87 (br. s, 1 H), 3.77 (br. s, 1 H), 3.68–3.60 (m, 3 H), 1.43 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 141.3, 138.5, 138.3, 128.2, 127.6, 127.5, 127.4, 127.3, 110.4, 80.6, 80.0, 79.9, 73.3, 73.2, 72.9, 66.9, 53.8, 46.3, 28.3 ppm. HRMS (ESI): calcd. for $C_{33}H_{39}NO_5$ [M + H]$^+$ 530.2906; found 530.2904.

Piperidine-1-carboxylates 24 and 25: Compound **23** (100 mg, 0.19 mmol) was dihydroxylated using the same procedure as that used to obtain **19** to give **24** and **25** in a ratio of 3:1 (100 mg, 94% yield), which were separated by silica gel column chromatography (hexane/ethyl acetate, 3:2).

***tert*-Butyl (2*S*,3*R*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate (24):** Yield: 75 mg, 70.7%. Viscous liquid. R_f = 0.5 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = –6.5 (*c* = 1.2, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3443, 2974, 1670, 1101 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.19 (m, 15 H, Ar*H*), 4.77 (d, *J* = 11.0 Hz, 1 H, OCH_2Ph), 4.71 (br. s, 1 H, OCH_2Ph), 4.58 (br. s, 2 H, OCH_2Ph), 4.53 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 4.43 (d, *J* = 12.2 Hz, 1 H, OCH_2Ph), 3.88–3.75 (m, 4 H), 3.71 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.59 (br. s, 1 H), 3.40 (br. d, *J* = 11.9 Hz, 1 H), 3.06 (br. s, 1 H), 2.94 (br. s, 1 H), 1.37 [s, 9 H,

C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 138.4, 138.1, 137.8, 128.4, 128.3, 127.8, 127.7, 127.5, 127.4, 84.4, 80.8, 77.9, 76.1, 73.3, 73.2, 72.8, 65.8, 63.8, 52.8, 44.5, 28.3 ppm. HRMS (ESI): calcd. for $C_{33}H_{41}NO_7$ [M + H]$^+$ 564.2961; found 564.2962.

***tert*-Butyl (2*S*,3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate (25):** Yield: 25 mg, 23.5%. Viscous liquid. R_f = 0.5 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = –11.4 (c = 1.0, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3446, 2927, 1681, 1100 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.23–7.17 (m, 15 H, Ar*H*), 4.83 (d, J = 11.0 Hz, 1H, OCH_2Ph), 4.62–4.52 (m, 3 H, OCH_2Ph), 4.46–4.37 (m, 2 H, OCH_2Ph), 4.04–3.97 (m, 2 H), 3.87–3.69 (m, 3 H), 3.37 (br. s, 1 H), 3.16 (br. s, 1 H), 3.06 (br. s, 1 H), 2.44 (br. s, 1 H), 1.46 [br. s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.1, 138.0, 137.9, 137.8, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 127.4, 80.1, 77.8, 75.1, 73.9, 73.1, 73.0, 67.2, 65.8, 53.3, 51.2, 46.4, 45.2 28.3 ppm. HRMS (ESI): calcd. for $C_{33}H_{41}NO_7$ [M + H]$^+$ 564.2961; found 564.2960.

(2*S*,3*R*,4*S*,5*R*)-2,5-Bis(hydroxymethyl)piperidine-3,4,5-triol (6): A solution of **24** (75 mg, 0.13 mmol) in methanol (5 mL) was stirred under H_2 in the presence of 10% Pd/C (35 mg) for 36 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and the filtrate concentrated. The residue was dissolved in methanol (2 mL), conc HCl (0.15 mL) was added and the mixture heated at 80 °C. After completion of the reaction, the reaction mixture was concentrated and the residue was passed through a Dowex (50X) basic resin column and concentrated under reduced pressure to give the iminosugar **6** (23 mg, 89.5% yield) as a viscous liquid. R_f = 0.2 (ethyl acetate: methanol, 4:1). $[\alpha]_D^{25}$ = +75.0 (c = 0.24, MeOH). ^{1}H NMR (500 MHz, D_2O): δ = 3.80 (m, 1 H), 3.72 (d, J = 3.5 Hz, 1 H), 3.62–3.69 (m, 2 H), 3.50 (d, J = 12.0 Hz, 1 H), 3.36 (d, J = 12.0 Hz, 1 H), 3.21 (dt, J = 6.0, 1.5 Hz, 1 H), 2.91 (s, 2 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 74.7, 70.6, 69.4, 66.6, 62.3, 58.4, 48.8 ppm. HRMS (ESI): calcd. for $C_7H_{15}NO_5$ [M + H]$^+$ 194.1028; found 194.1026.

(2*S*,3*R*,4*S*,5*R*)-[5-Acetoxy-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-piperidin-5-yl]methyl Acetate (26): Ac_2O (0.012 mL, 0.13 mmol), Et_3N (0.02 mL, 0.13 mmol), and a catalytic amount of DMAP were added to a stirred solution of compound **24** (25 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) cooled to 0 °C. After stirring for 2 h at room temperature, the usual work-up and chromatographic purification afforded the diacetate, which was used directly for further reaction. The residue was taken in CH_2Cl_2 (1 mL), cooled to 0 °C, and trifluoroacetic acid (0.05 mL) was added. After stirring for 2 h, the reaction mixture was neutralized with aq. Na_2CO_3 and extracted with CH_2Cl_2. Purification by column chromatography afforded the pure compound **26** (20.5 mg, 84.3% yield) as a colorless liquid. R_f = 0.4 (hexane/ethyl acetate, 1:2). IR (neat): $\tilde{\nu}$ = 3427, 2922, 1713, 1093 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 15 H, Ar*H*), 4.69 (d, J = 2.5 Hz, 1 H, 4-H), 4.68 (d, J = 12.0 Hz, 1 H), 4.56–4.51 (m, 3 H), 4.47 (d, J = 12.0 Hz, 1 H), 4.39 (d, J = 11.0 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 4.30 (d, J = 11.0 Hz, 1 H), 3.55–3.46 (m, 3 H, 3-H, 7-H, 7′-H), 3.27 (t, J = 5.5 Hz, 1 H, 2-H), 3.09 (d, J = 14.0 Hz, 1 H, 6e-H), 2.93 (d, J = 14 Hz, 1 H, 6a-H), 2.0 (s, 3 H, COCH_3), 1.6 (s, 3 H, COCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 170.6, 138.1, 137.7, 137.3, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 78.2, 73.5, 73.3, 73.2, 72.7, 63.8, 53.8, 48.2, 21.8, 20.7 ppm. HRMS (ESI): calcd. for $C_{32}H_{37}NO_7$ [M + H]$^+$ 548.2648; found 548.2645.

***tert*-Butyl (2*S*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-methylenepiperidine-1-carboxylate (29):** Compound **29** (258 mg, 83.7% yield) was obtained as a viscous liquid from **27** (250 mg, 0.58 mmol) by following the same procedure as that used to obtain **23**. R_f = 0.6 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{25}$ = +21.6 (c = 0.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2925, 1693, 1412 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 15 H, Ar*H*), 5.22 (s, 1 H, olefinic), 5.13 (s, 1 H, olefinic), 4.64–4.56 (m, 5 H), 4.46–4.40 (m, 3 H), 4.16 (br. s, 1 H), 3.91 (br. s, 1 H), 3.58–3.53 (m, 3 H), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 139.6, 138.4, 138.0, 128.2, 127.8, 127.3, 111.0, 79.8, 76.4, 74.5, 73.0, 71.4, 70.6, 68.7, 54.2, 46.3, 28.4 ppm. HRMS (ESI): calcd. for $C_{33}H_{39}NO_5$ [M + H]$^+$ 530.2906; found 530.2904.

***tert*-Butyl (2*S*,3*S*,4*S*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate (30):** Diol **30** (263 mg, 98.8% yield) was obtained as a viscous liquid from compound **29** (250 mg, 0.47 mmol) using the same procedure as that used to obtain **19**. R_f = 0.5 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = +61.4 (c = 0.9, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3433, 2925, 1685, 1100 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 15 H, Ar*H*), 4.64–4.62 (m, 1 H, OCH_2Ph), 4.47–4.40 (m, 5 H, OCH_2Ph), 4.03 (br. d, J = 13.6 Hz, 1 H), 3.88 (br. s, 1 H), 3.70 (d, J = 2.9 Hz, 1 H), 3.57–3.50 (m, 2 H), 2.67–2.60 (m, 5 H), 1.39 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 138.1, 137.8, 128.5, 128.4, 128.3, 127.8, 127.7, 127.5, 81.6, 80.6, 74.1, 73.3, 73.2, 72.7, 71.9, 68.1, 64.9, 54.8, 46.0, 28.2 ppm. HRMS (ESI): calcd. for $C_{33}H_{41}NO_7$ [M + H]$^+$ 564.2961; found 564.2963.

***tert*-Butyl (2*S*,3*S*,4*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-oxopiperidine-1-carboxylate (31):** $NaIO_4$ (57 mg, 0.27 mmol) dissolved in water was added to a solution of diol **30** (100 mg, 0.18 mmol) in methanol (2 mL) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. Water was added to the reaction mixture and the solvent was 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 **31** (95 mg, 95%) as a colorless oil. R_f = 0.7 (hexane/ethyl acetate, 7:3). $[\alpha]_D^{25}$ = +17.1 (c = 0.4, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1740, 1696, 1120 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 14 H, Ar*H*), 7.14 (d, J = 7.5 Hz, 1 H, Ar*H*), 4.83 (d, J = 12.4 Hz, 1 H, OCH_2Ph), 4.64 (br. s, 2 H), 4.54 (d, J = 12.4 Hz, 1 H, OCH_2Ph), 4.49–4.39 (m, 2 H), 4.36 (br. s, 3 H), 4.10 (br. s, 1 H), 3.82 (br. d, J = 16.3 Hz, 1 H), 3.64 (br. s, 1 H), 3.57 (dd, J = 3.2, 9.7 Hz, 1 H), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 154.5, 137.7, 137.6, 137.5, 128.5, 128.4, 128.3, 127.8, 127.6, 127.4, 80.8, 79.6, 76.6, 73.4, 72.5, 71.8, 69.2, 54.0, 28.3 ppm. HRMS (ESI): calcd. for $C_{32}H_{37}NO_6$ [M + H]$^+$ 532.2699; found 532.2696.

***tert*-Butyl (2*S*,3*S*,4*R*,5*R*)-5-Acetoxy-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidine-1-carboxylate (32):** $NaBH_4$ (22 mg, 0.57 mmol) was added to a stirred solution of compound **31** (200 mg, 0.38 mmol) in methanol (4 mL) cooled to 0 °C. The reaction mixture was stirred at same temperature for 30 min and then quenched with a saturated NH_4Cl solution. The reaction mixture was concentrated under high vacuum to remove methanol. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with water and brine and dried with anhydrous Na_2SO_4. After concentration, the crude residue was directly subjected to acetylation in dry DCM (2 mL) using Ac_2O, Et_3N, and a catalytic amount of DMAP. After stirring for 4 h at room temperature, the usual work-up and chromatographic purification afforded acetate **32** (173 mg, 80%) as a colorless liquid. R_f = 0.6 (hexane/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = +12.4 (c = 0.8, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1736, 1696, 1244, 1172 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.17 (m 15 H, Ar*H*), 5.12 (br. s, 1 H, 5-H), 4.75

(br. s, 1 H, 2-H), 4.69–4.65 (m, 2 H, OCH_2Ph), 4.61 (d, J = 12.4 Hz, 1 H, OCH_2Ph), 4.53 (d, J = 12.4 Hz, 1 H, OCH_2Ph), 4.40–4.39 (m, 2 H, OCH_2Ph), 4.33 (br. d, J = 15.2 Hz, 1 H, 6′-H), 3.85 (t, J = 2.6 Hz, 1 H, 3-H), 3.76 (t, J = 3.6 Hz, 1 H, 4-H), 3.50–3.49 (m, 2 H, 7-H, 7′-H), 3.08 (br. d, J = 14.8 Hz, 1 H, 6-H), 2.04 (s, 3 H, OCH_3), 1.41 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.1, 171.1, 155.5, 138.9, 138.2, 137.8, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 79.9, 74.1, 73.7, 73.2, 71.6, 71.0, 69.4, 67.4, 53.9, 43.5, 28.3, 21.2 ppm. HRMS (ESI): calcd. for $C_{34}H_{41}NO_7$ [M + H]$^+$ 576.2961; found 576.2961.

(2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)piperidine-3,4,5-triol Hydrochloride (4): Hydrogenolysis (10% Pd/C) of compound **32** (50 mg, 0.09 mmol) in methanol gave the debenzylated compound, which was passed through a pad of Celite. The filtrate was concentrated and the residue was dissolved in 6 N aqueous HCl and refluxed for 4 h. Solvent removal afforded **4** (15 mg, 86%) as a white solid. R_f = 0.4 (ethyl acetate/methanol, 4:1); m.p. 165 °C. $[a]_D^{25}$ = –37.5 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, D_2O): δ = 4.03 (t, J = 2.5 Hz, 1 H), 3.87 (ddd, J = 2.5, 5.0, 11.5 Hz, 1 H), 3.80 (dd, J = 3.0, 13.0 Hz, 1 H), 3.72 (dd, J = 5.5, 13.0 Hz, 1 H), 3.69 (dd, J = 2.5, 11.0 Hz, 1 H), 3.17–3.21 (m, 1 H), 3.12 (dd, J = 5.5, 12.5 Hz, 1 H), 2.98 (t, J = 11.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.4, 67.8, 67.0, 60.1, 57.2, 44.0 ppm. HRMS (ESI): calcd. for $C_6H_{14}ClNO_4$ [M + H]$^+$ 164.0923; found 164.0923.

Supporting Information (see also the footnote on the first page of this article): Spectra of the new compounds **4**–**6**, **9**, **10**, **12**, **14**–**26**, and **29**–**32**.

Acknowledgments

We thank the Department of Science and Technology (DST), New Delhi for financial support to Y. D. V. in the form of a Ramanna Fellowship (Grant No. SR/S1/RFOC-04/2006). P. G. thanks the University Grants Commission, New Delhi for a Senior Research Fellowship.

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Received: December 31, 2008
Published Online: March 5, 2009

