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$InCl_3$–CH_3CN–H_2O: an efficient catalyst-solvent combination for the synthesis of Perlin aldehydes and related compounds. Application in the synthesis of unnatural L-azasugars

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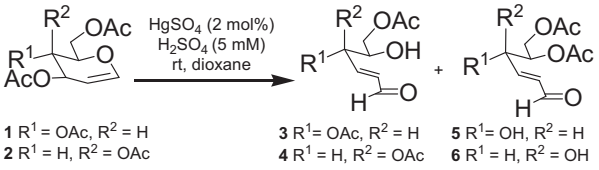
ABSTRACT

$InCl_3$–CH_3CN–H_2O has been found to be an efficient catalyst-solvent combination for the synthesis of Perlin aldehydes and related compounds. While acetylated glycals afforded the Perlin aldehydes directly with $InCl_3$ and water, benzylated glycals on the other hand provided the hemiacetals under identical condition. The methodology reports a non-mercurial approach to Perlin aldehydes. Noteworthy is that this reaction is more facile as well as highly selective with glycals possessing a hydroxyl as a leaving group than with a benzyloxy group. Extension of this reaction to 2-*C*-hydroxymethyl glycals resulted in the formation of the corresponding hemiacetals, which were further transformed in to unsaturated azasugars with an *exo*-methylene group at *C*-2 position. Glycosidase inhibition studies reveal that these compounds display selectivity in inhibiting glucosidases rather than galactosidases.

1. Introduction

Carbohydrate derived chiral intermediates have found enormous applications in organic synthesis due to their inherent functional group, stereochemical and structural diversities as well as their ready availability.[1] It has been well documented that the presence of a push–pull α,β-unsaturated carbonyl group further enhances the versatility of sugar nuclei as chiral templates in organic synthesis. Examples of such compounds include alkyl-hex-2-eno-uloses,[2] 2-*C*-formyl glycals,[3] 2,3-dideoxy-α,β-unsaturated sugar aldehydes[4,5] and other carbohydrate based enones.[6] Since last three decades, 2,3-dideoxy-α,β-unsaturated sugar aldehydes, popularly known as Perlin aldehydes, have been serving as attractive precursors for the synthesis of a wide array of biologically important natural and unnatural compounds.[7–20] Conventionally, Perlin aldehydes are prepared by oxymercuration–demercuration reaction of suitably protected glycals in the presence of 5mM sulfuric acid (Scheme 1).[4] Perlin reported that tri-*O*-acetyl-D-glucal **1** on reaction with 2 mol % of $HgSO_4$ in presence of 0.01–0.02 N H_2SO_4 afforded the corresponding α,β-unsaturated aldehyde **3** along with an inseparable side product **5**, arising out of an acyl migration from *C*-4 to *C*-5 carbon of **3** (Scheme 1). Similar reaction was observed with tri-*O*-acetyl-D-galactal **2** also.



1 R^1 = OAc, R^2 = H
2 R^1 = H, R^2 = OAc
3 R^1 = OAc, R^2 = H
4 R^1 = H, R^2 = OAc
5 R^1 = OH, R^2 = H
6 R^1 = H, R^2 = OH

Scheme 1. Synthesis of Perlin aldehydes using $HgSO_4/H_2SO_4$.

A couple of modified procedures developed later also rely on the use of toxic Hg^{2+} salts.[5,21] Further, a reinvestigation of the oxymercuration–demercuration reaction of glycals by Shaw and co-workers revealed that the reaction was highly solvent (THF vs dioxane) dependent.[21] The only non-mercurial method available as of now for the synthesis of Perlin aldehydes is also due to Shaw and co-workers.[22] They had reported that exposure of diversely protected glycals to a mixed Lewis acid ($HfCl_4$ and ZnI_2) catalyst at room temperature to 140 °C resulted in the facile formation of the corresponding Perlin aldehydes **9** and **10** (Scheme 2). Notable observation was that the reaction required both the Lewis acids and was unsuccessful with either of them only. Moreover, in case of benzyl and methyl protected glycals, the corresponding 2-deoxy-hexoses **11** were obtained in considerable proportions.

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† Contributed in bio-assay studies.

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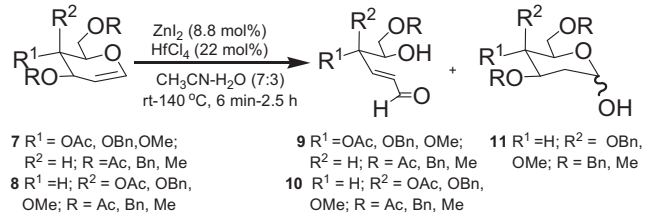
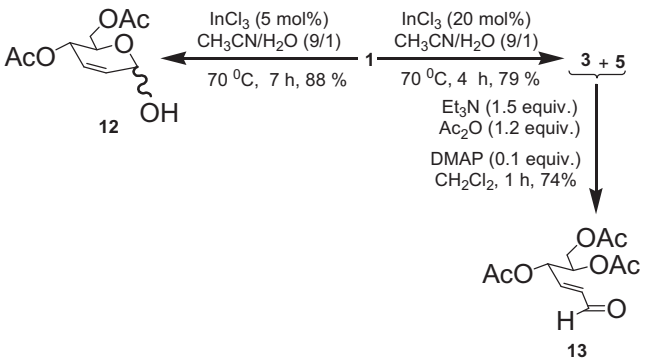
In view of the growing importance of Perlin aldehydes as versatile chiral substrates in organic synthesis, it was thought that development of a new methodology, complementary to the existing ones, would be of significance. As a part of our ongoing research on the use of $InCl_3$ as a mild Lewis acid catalyst for various transformations in carbohydrate chemistry,[23,24] we explored its utility towards the synthesis of Perlin aldehydes and related compounds. Our results in this direction are reported here. We have also extended the reaction to 2-*C*-hydroxymethyl glycals **22** and **23**, and the resulting hemiacetals were further transformed to unnatural azasugars.



Scheme 2. Synthesis of Perlin aldehydes using a mixed Lewis acid ($HfCl_4$ and ZnI_2) catalyst.

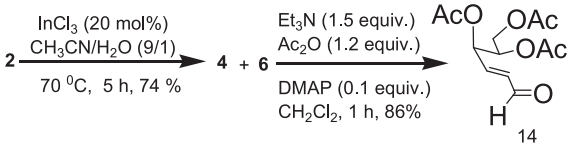
2. Results and discussion

Our initial studies began with the reaction of tri-*O*-acetyl-D-glucal **1** with water, in acetonitrile as a solvent, in presence of 5 mol % of $InCl_3$ as a catalyst at room temperature. Though a new product was formed (vide TLC), the reaction did not go to completion even after a long time. Complete consumption of the starting material was noticed when the reaction was performed for 7 h at 70 °C with 5 mol % of $InCl_3$ in acetonitrile and water (9:1). However, it was observed that the isolated product was not the expected Perlin aldehyde **3** as revealed by the absence of the signal due to the aldehydic proton in its ^1H NMR spectrum. Detailed analysis of the spectral data led to its identification as the unsaturated hemiacetal **12** arising out of $InCl_3$ catalyzed Ferrier rearrangement of tri-*O*-acetyl-D-glucal with water (Scheme 3).[25] Prolonged reaction time did not lead to any appreciable conversion of the cyclic hemiacetal **12** to the open-chain Perlin aldehyde **3**. Subsequently, upon increasing the amount of the catalyst from 5 to 20%, the expected Perlin aldehyde **3** could be obtained along with another isomer **5** arising from the migration of the acetyl group from *C*-4 carbon to *C*-5 carbon in a ratio of 60:40. In order to confirm that compounds **3** and **5** are positional isomers, the inseparable mixture of **3** and **5** was acetylated with acetic anhydride in the presence of Et_3N and catalytic amount of DMAP to get the single triacetate **13** in 74% yield whose spectral data were identical with those of the literature reported values (Scheme 3).[4,21]



Scheme 3. $InCl_3$ catalyzed synthesis of Perlin aldehyde from tri-*O*-acetyl-D-glucal **1**.

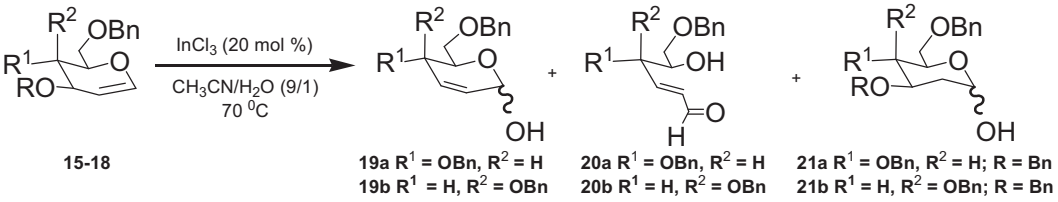
The reaction was also successful with tri-*O*-acetyl-D-galactal **2** and the α,β-unsaturated aldehyde **4** was obtained in 5 h along with compound **6** in a ratio of 70:30 with an overall yield of 74%. As before, acetylation of the mixture afforded the triacetate **14** in 86% yield (Scheme 4).



Scheme 4. $InCl_3$ catalyzed synthesis of Perlin aldehyde from tri-*O*-acetyl-D-galactal **2**.

The reaction of tri-*O*-benzyl-D-glucal **15** with $InCl_3$ in acetonitrile and water required a slightly longer time (8 h) to go to completion, under identical condition. In this case, even with 20 mol % of the catalyst, hemiacetal **19a** was obtained as the major product with only a trace amount (~<10%) of the α,β-unsaturated aldehyde **20a**, as could be seen from the ^1H NMR spectrum of the crude reaction mixture (Scheme 5, Table 1, entry 1). All our efforts to direct the reaction exclusively towards the Perlin aldehyde **20a** were in vain. This observation indicates that in the reaction of acetyl protected glycals **1** and **2** with water (Schemes 3 and 4), the acetic acid, that is, formed as the by-product plays a crucial role in catalyzing the further transformation of the hemiacetal to Perlin aldehyde. On the other hand, with tri-*O*-benzyl-D-glucal **15** as the substrate, the by-product benzyl alcohol is a neutral compound. It is likely that in the absence of a strong acid, the reaction could not proceed further towards Perlin aldehyde and $InCl_3$ alone may not be enough to catalyze the reaction completely resulting in its formation only in a trace amount. While a couple of methods are available for the direct synthesis of the Perlin aldehyde **20a** from tri-*O*-benzyl-D-glucal **15**, to our knowledge, there is no practical method available for the synthesis of the hemiacetal **19a** as of today. It was obtained only as a by-product in the enantioselective oxidation reaction of olefins from the corresponding sugar peroxides.[26] Hall and co-workers have reported the synthesis of the hemiacetal **19a** in only 20% from the reaction of ethyl 4,6-di-*O*-benzy1-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with chlorosulfonyl isocyanate.[27] The present methodology thus offers a convenient protocol for the synthesis of the hemiacetal **19a**.

The reaction of tri-*O*-benzyl-D-galactal **16** with 20 mol % of $InCl_3$ was sluggish and took 18 h for completion to give a mixture of the hemiacetal **19b** and the corresponding 2-deoxygalactose **21b** in almost equal proportion with an overall yield of 52% only (Scheme 5, Table 1, entry 2). This is not surprising, as it is well documented in literature that during the Ferrier rearrangement of protected galactals, the corresponding 2-deoxy products were invariably formed in considerable amounts.[22,28] Formation of 2-deoxygalactose **21b** even during the synthesis of Perlin aldehyde **20b** from tri-*O*-benzyl-D-galactal **16** was generally inevitable[22] and the reaction was solvent dependant as reported by Shaw and co-workers.[21] Encouraged by our recent finding[24b] on the efficient $InCl_3$ catalyzed Ferrier rearrangement of 4,6-di-*O*-benzyl-D-galactal **17** with alcohols and that too without the formation of the corresponding 2-deoxygalactoside, we examined the behaviour of **17**[29] with water in presence of $InCl_3$ in CH_3CN at 70 °C. Quite surprisingly, the reaction was found to be quite fast and complete consumption of starting material was noticed in just 2 h (as compared to 18 h with tri-*O*-benzyl-D-galactal **16**). More so even, the reaction *exclusively* afforded the hemiacetal **19b** in 86% yield without the formation of 2-deoxygalactose **21b** (Scheme 5, Table 1, entry 3). The reaction was also found to be facile with 4,6-di-*O*-benzyl-D-glucal[30] **18** (Scheme 5, Table 1, entry 4). These reactions, typically involving a [1,3]-allylic transposition of hydroxyl group, provide a ready access to sugar



Scheme 5. $InCl_3$ catalyzed reaction of benzylated glycals **15**–**18** with water in acetonitrile solvent.

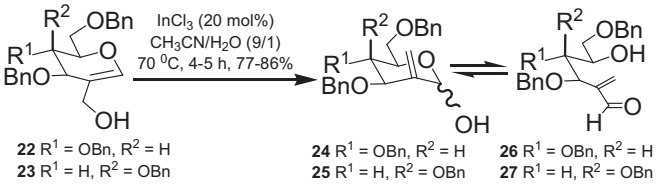
Table 1
$InCl_3$ catalyzed reaction of benzylated glycals **15**–**18** with water in acetonitrile solvent

Entry	Glycal	R^1	R^2	R	Time (h)	Ratio of Products			Yield[a] (%)
						19	**20**	**21**	
1	**15**	OBn	H	Bn	8	92	8	0	72
2	**16**	H	OBn	Bn	18	52	0	48	52
3	**17**	H	OBn	H	2	89	11	0	86
4	**18**	OBn	H	H	3	96	4	0	77

[a] overall isolated yield after column chromatography.

hemiacetals, for which a convenient method has remained elusive so far especially with benzylated glycals. Moreover, these observations further strengthen our earlier findings that $InCl_3$ has a greater affinity to coordinate with a hydroxyl group over an alkyl or acyl group.[24]

Extension of this reaction to 2-*C*-hydroxymethyl glycals **22** and **23**[31] afforded the corresponding 2-*C*-methylene hexoses **24** and **25** in 5 h and 4 h, respectively, in good yields (Scheme 6). In these examples, the unsaturated hemiacetals **24** and **25** were found to be in equilibrium with their open-chain α,β-unsaturated aldehydes **26** and **27**. Interesting observation is that while in case of glucal **22** the equilibrium is in favour of the hemiacetal **24** (**24**/**26**=89:11), it was the other way in the galactal **23** with the α,β-unsaturated aldehyde **27** being the predominant one (**25**/**27**=1:2).



Scheme 6. $InCl_3$ catalyzed reaction of 2-*C*-hydroxymethyl glycals with water in acetonitrile solvent.

Chemistry and biology of naturally occurring iminosugars (azasugars) and their synthetic analogues continue to be in the forefront of the inter-disciplinary research domain of glycobiology for over four decades.[32] Their significant and selective inhibition of various glycosidases make them attractive lead molecules against various carbohydrate-mediated disorders such viral, diabetes, HIV, etc.[33] The selective glycosidase inhibition property is attributed to their structural resemblance as well as mimicry of glycosidase oxocarbenium-ion-like transition state.[34] Azasugar based drugs such as Zavesca® **30** and Glyset® **31** (Fig. 1) are already in clinical use for the treatment of diabetes, Gaucher's disease, etc.[33] In continuation of our work on the synthesis of natural and novel unnatural azasugars,[35] it was envisaged that the hemiacetals **24** and **25** would be ideal substrates for the synthesis of 2-*C*-methylene-azasugars through cleavage of the *O*-C_1 bonds of **24** and **25** followed by cyclization with amines.

Reduction of an equilibrium mixture of **25** and **27** with 1.5 equiv of $NaBH_4$ at room temperature afforded the unsaturated diol **32** in 85% yield in 30 min. Mesylation of **32** with 2.2 equiv of mesyl chloride in presence Et_3N at 0 °C yielded the dimesylate **33** in 2 h (85%

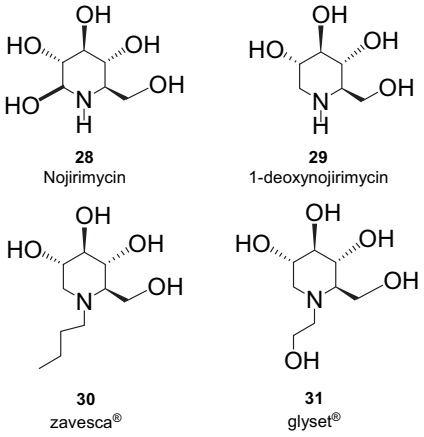
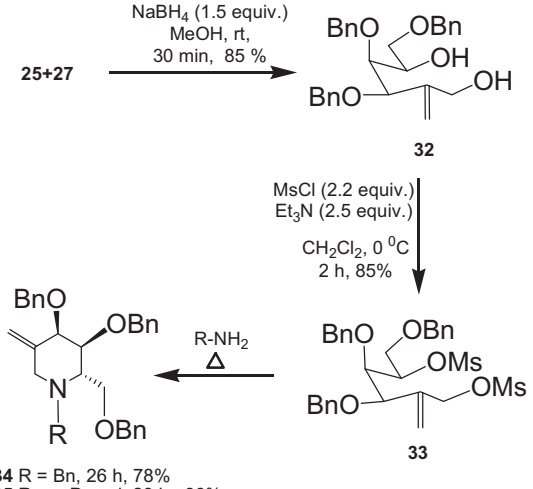


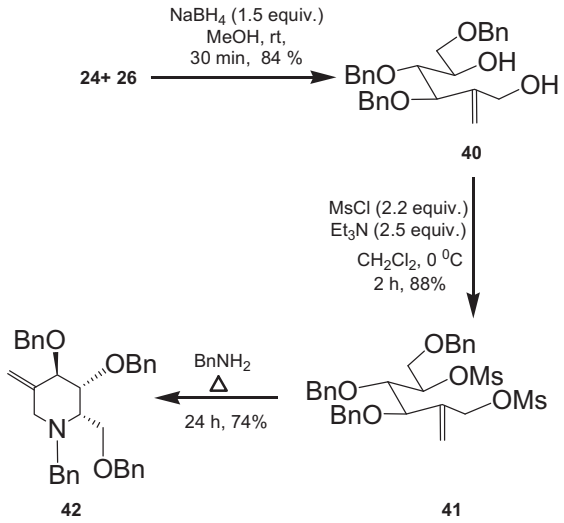
Fig. 1. Representative examples of six-membered azasugars.

crude yield). Upon heating with benzylamine for 26 h at 90 °C, the dimesylate underwent a double nucleophilic substitution reaction to afford the protected azasugar derivative **34** as a single diastereomer in 78% yield (Scheme 7).[36] Gupta and Vankar recently reported,[37] through a facile and a novel in situ aza Claisen rearrangement of trichloroacetamidate derivative of 2-*C*-hydroxymethyl-D-galactal, the synthesis of azasugar **34** in seven steps from 2-*C*-hydroxymethyl-D-galactal **23**. While providing an alternative to Vankar's method, the present route is also versatile enough to introduce diverse substituents on the ring nitrogen by way of utilizing different amines during the cyclization step. Thus, the generality of the cyclization reaction was demonstrated by heating the dimesylate **33** with a few other amines and the corresponding protected azasugars **35**–**39** were obtained in good yields (Scheme 7).



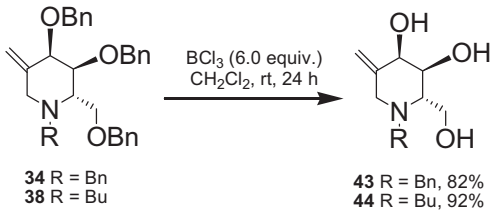
Scheme 7. Synthesis of unsaturated azasugars **34**–**39** from 2-*C*-hydroxymethyl-D-galactal **23**.

Extension of the synthetic sequence to 2-*C*-hydrxoymethyl-D-glucal **22** resulted in the formation of the unsaturated azasugar **42**, (Scheme 8).



Scheme 8. Synthesis of unsaturated azasugar **42** from 2-*C*-hydroxymethyl-D-glucal **22**.

Deprotection of azasugars **34** and **38** was next carried out with a view to studying the glycosidase inhibitory properties of these classes of compounds. Selective O-debenzyaltion[38] of compound **34** was achieved by exposing it to 6.0 equiv of BCl_3 in CH_2Cl_2 at room temperature to get the hitherto unreported azasugar analogue **43** in 82% yield. Both the *N*-benzyl as well the *exo*-methylene groups remain unaffected during this deprotection step. Similar reaction with *N*-butyl derivative **38** afforded the corresponding new L-azasugar derivative **44** in 92% yield (Scheme 9).



Scheme 9. Deprotection of compounds **34** and **38**.

Compounds **43** and **44** were tested for their inhibitory activities against four different commercially available enzymes (Table 2).[35b] They did not show any inhibition against α- and β-galactosidases. Compound **43** displayed inhibition against both α- and β-glucosidases with IC_{50} values of 4.5 mM and 8.2 mM, respectively. On the other hand, compound **44** displayed selectivity by inhibiting only β-glucosidase with an IC_{50} value of 7.5 mM and not the α-glucosidase.

Table 2
Inhibition studies of compounds **43** and **44**

Entry	Enzyme	Source	Condition	IC_{50}, mM	
				43	**44**
1	α-Glucosidase	Baker's yeast (type I)	37 °C, pH=6.8	4.5	8.2
2	β-Glucosidase	Almond	37 °C, pH=5	7.5	NI
3	α-Galactosidase	Green coffee beans	25 °C, pH=6.5	NI	NI
4	β-Galactosidase	*E. coli*	37 °C, pH=7.3	NI	NI

NI=no inhibition was observed up to 10 mM inhibitor concentration.

3. Conclusions

In conclusion, we have found that $InCl_3$–CH_3CN–H_2O is an efficient catalyst-solvent combination for the synthesis of Perlin aldehyde and related compounds. With acylated glycals the α,β-unsaturated aldehydes (Perlin aldehydes) were obtained directly, while benzylated glycals afforded the corresponding hemiacetals. We have extended this reaction to 2-*C*-hydroxymethyl glycals to get a new class of unsaturated carbohydrate derived hemiacetals. Application of our methodology towards the synthesis of unsaturated azasugars has been highlighted. The glycosidase inhibitions activities of these compounds show promising future for developing new unsaturated azasugars with better inhibition properties. Further functionalization of the exocyclic double bonds of compounds **34**–**39** and **42** is in progress. Their synthesis and biological activities will form part of our future work in this area.

4. Experimental section

4.1. General considerations

All solvents were purified by standard procedures. Thin-layer chromatography (TLC) was performed on Merck silica gel precoated on aluminium plates. Flash column chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on an Autopol V (Rudolph Research Flanders, New Jersey) instrument. All the rotations were measured at 589 nm (sodium D line). IR spectra were taken over the 4000–400 cm^{-1} range as KBr pellets on a Nicolet (Madison, USA) FTIR spectrophotometer (Model Protégé 460). All the ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker Spectrospin DPX FT-NMR spectrometer. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as internal standard. Mass spectra were recorded with an Applied Biosystems Q-Star instrument.

4.2. 4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranose 12

Glycal **1** (0.272 g, 1 mmol) was dissolved in a 10 mL mixture of acetonitrile and water (9:1). After 5 min, $InCl_3$ (0.011 g, 0.05 mmol) was added and the reaction mixture was stirred at 70 °C for 7 h. It was then quenched with water and extracted with chloroform (3×50 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography over silica gel using hexane/ethyl acetate (4:1) afforded the hemiacetal **12** as a viscous colourless liquid in 88% yield (0.202 g). The spectral data of compound **12** were found to be identical with the literature reported values.[25]

4.3. General procedure for the synthesis of Perlin aldehydes from acylated glycals 1 and 2

Glycal **1** or **2** (1 mmol) was dissolved in a 10 mL mixture of acetonitrile and water (9:1). After 5 min, $InCl_3$ (0.20 mmol) was added and the reaction mixture was stirred at 70 °C for 4–5 h. It was then quenched with water and extracted with chloroform (3×50 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography over silica gel using hexane/ethyl acetate (4:1) afforded the corresponding Perlin aldehydes.

*4.3.1. Synthesis of (2E)-4,6-di-O-acetyl-2,3-dideoxy-D-erythro-hex-2-enose **3**.* Compound **3** was obtained along with **5** (0.335 g, 79% yield) in 4 h as a colourless viscous liquid by the reaction of glycal **1** (0.500 g, 1.83 mmol) with $InCl_3$ (0.081 g, 0.367 mmol). The spectral

data of compounds **3** and **5** were found to be identical with the literature reported values.[4,25]

*4.3.2. Synthesis of (2E)-4,6-di-O-acetyl-2,3-dideoxy-D-threo-hex-2-enose **4**.* Compound **4** was obtained along with **6** (0.240 g, 74% yield) in 5 h as a colourless viscous liquid by the reaction of glycal **2** (0.380 g, 1.40 mmol) with $InCl_3$ (0.062 g, 0.28 mmol). The spectral data of compounds **4** and **6** were found to be identical with the literature reported values.[4,25]

4.4. Synthesis of (2*E*)-4,5,6-tri-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose 13

A mixture of compounds **3** and **5** (0.099 g, 0.430 mmol) was dissolved in dry dichloromethane (10 mL). Triethylamine (0.091 mL, 0.645 mmol) was added to the reaction mixture, followed by DMAP (0.006 g, 0.0430 mmol) and acetic anhydride (0.049 mL, 0.516 mmol) and the reaction mixture was stirred at room temperature. After 1 h, when the reaction was found to be completed, the reaction mixture was quenched with ammonium chloride solution (100 mL) and extracted with chloroform (3×50 mL). The organic layer was washed with aqueous saturated bicarbonate solution and then dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography over silica gel using hexane/ethyl acetate (6:1) afforded the triacetate **13** as a colourless viscous liquid in 74% yield (0.086 g). The spectral data of compound **13** were found to be identical with the literature reported values.[4,25]

4.5. Synthesis of (2*E*)-4,5,6-tri-*O*-acetyl-2,3-dideoxy-D-*threo*-hex-2-enose 14

Compound **14** (0.243 g, 86% yield) was obtained (following the same procedure as for **13**) by the reaction of a mixture of **4** and **6** (0.240 g, 1.04 mmol), triethylamine (0.219 mL, 1.56 mmol), DMAP (0.013 g, 0.104 mmol) and acetic anhydride (0.117 mL, 1.24 mmol). The spectral data of compound **14** were found to be identical with the literature reported values.[4,25]

4.6. General procedure for the synthesis of unsaturated hemiacetals from benzylated glycals 15–18, 22, 23

Glycals **15**–**18** or **22** or **23** (1 mmol) was dissolved in a 10 mL mixture of acetonitrile and water (9:1). After 5 min, $InCl_3$ (0.020 mmol) was added and the reaction mixture was stirred at 70 °C for appropriate time. It was then quenched with water and extracted with chloroform (3×50 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated. Purification by column chromatography over silica gel using hexane/ethyl acetate (4:1) afforded the corresponding hemiacetals.

*4.6.1. 4,6-Di-O-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranose **19a**.* Compound **19a** (0.175 g, 72% yield) was obtained in 8 h as a colourless viscous liquid from the reaction of 3,4,6-tri-*O*-benzyl-D-glucal **15** (0.31 g, 0.745 mmol) with $InCl_3$ (0.032 g, 0.143 mmol). Alternatively, compound **19a** (0.093 g, 77% yield) was also obtained in 3 h as a colourless viscous liquid from the reaction of 4,6-di-*O*-benzyl-D-glucal **18** (0.120 g, 0.368 mmol) with $InCl_3$ (0.016 g, 0.0736 mmol). R_f (30% EtOAc/hexane) 0.24. Specific rotation reported here is for the mixture of hemiacetal **19a** and aldehyde **20a** present in a ratio of 96:4; $[\alpha]_D^{28}$ +70.5 (*c* 0.38, $CHCl_3$); ν_{max} (KBr) 3394, 3033, 2911, 2862, 1686, 1452, 1388, 1307, 1247, 1204, 1072, 1026, 939, 740, 693, 611 cm^{-1}; ^1H and ^{13}C NMR values reported here correspond to the signals of hemiacetal **19a** taken from a mixture of hemiacetal **19a** and aldehyde **20a**; δ_H (300 MHz, $CDCl_3$) 7.32–7.25 (10H, m, aromatic), 6.07 (1H, d, *J*=10.8 Hz, H-2), 5.79 (1H, d, *J*=10.8 Hz, H-3), 5.41 (1H, br s, H-1), 4.61 (1H, d, *J*=12.0 Hz, $-OCH_2Ph$), 4.60 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.51 (1H, d, *J*=12.0 Hz, $-OCH_2Ph$), 4.44 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.10 (2H, br s), 3.69 (2H, br s);δ_C (75 MHz, $CDCl_3$) δ 137.8, 130.2, 130.0, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4, 90.9, 88.8, 73.2, 70.9, 70.2, 68.8; HRMS (ESI): $[M+Na]^+$ found 349.1399. $C_{20}H_{22}O_4Na$ requires 349.1416.

*4.6.2. 4,6-Di-O-benzyl-2,3-dideoxy-D-threo-hex-2-enopyranose **19b**.* Compound **19b** (0.182 g, 56% yield) was obtained in 18 h as a colourless viscous liquid from the reaction of 3,4,6-tri-*O*-benzyl-D-galactal **16** (0.420 g, 1.009 mmol) with $InCl_3$ (0.044 g, 0.201 mmol). Alternatively, compound **19b** (0.086 g, 86% yield) was also obtained in 2 h as a colourless viscous liquid from the reaction of 4,6-di-*O*-benzyl-D-galactal **17** (0.100 g, 0.306 mmol) with $InCl_3$ (0.013 g, 0.061 mmol). R_f (30% EtOAc/hexane) 0.28. Specific rotation reported here is for a mixture hemiacetal **19b** and aldehyde **20b** present in a ratio of 89:11; $[\alpha]_D^{28}$ −84.2 (*c* 0.38, $CHCl_3$); ν_{max} (KBr) 3426, 3087, 3063, 2926, 2880, 1741, 1687, 1496, 1453, 1399, 1260, 1201, 1095, 1058, 1026, 951, 907, 736, 696 cm^{-1}; ^1H and ^{13}C NMR values reported here correspond to the signals of only hemiacetal **19b** taken from a mixture of hemiacetal **19b** and aldehyde **20b**; δ_H (300 MHz, $CDCl_3$) 7.37–7.33 (10H, m, aromatic), 6.14 (1H, dd, *J*=10.2, 5.4 Hz, H-2), 6.05 (1H, d, *J*=10.2 Hz, H-3), 5.52 (1H, br s, H-1), 4.68–4.42 (4H, m), 3.85–3.53 (4H, m).; δ_C (75 MHz, $CDCl_3$) 138.2, 137.9, 130.4, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 126.4, 88.4, 73.3, 70.8, 69.4, 69.2, 67.0; HRMS (ESI): $[M+Na]^+$ found 349.1405. $C_{20}H_{22}O_4Na$ requires 349.1416.

*4.6.3. 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-D-arabino-hexopyranose **24**.* Compound **24** (0.210 g, 77% yield) was obtained in 5 h as a colourless viscous liquid from the reaction of 3,4,6-tri-*O*-benzyl-2-*C*-hydroxymethyl-D-glucal **22** (0.272 g, 0.607 mmol) with $InCl_3$ (0.027 g, 0.121 mmol). R_f (30% EtOAc/hexane) 0.35. Specific rotation reported here is for a mixture hemiacetal **24** and aldehyde **26** present in a ratio of 89:11; $[\alpha]_D^{28}$ +5.8 (*c* 1.00, $CHCl_3$); ν_{max} (KBr) 3411, 3031, 2919, 2866, 1609, 1499, 1455, 1359, 1208, 1103, 1019, 918, 740, 697 cm^{-1}; ^1H and ^{13}C NMR values reported here correspond to the signals of only hemiacetal **24** taken from a mixture of hemiacetal **24** and aldehyde **26**;δ_H (300 MHz, $CDCl_3$) 7.35–7.15 (15H, m, aromatic), 5.54 (1H, s, $=CH_2$), 5.32 (1H, s, $=CH_2$), 5.13 (1H, s, H-1), 4.86 (1H, d, *J*=10.8 Hz, $-OCH_2Ph$), 4.73 (1H, d, *J*=11.1 Hz, $-OCH_2Ph$), 4.67 (1H, d, *J*=11.1 Hz, $-OCH_2Ph$), 4.60–4.53 (4H, m), 4.21 (1H, m), 3.86 (1H, br s), 3.64 (2H, m), 3.47 (1H, m); δ_C (75 MHz, $CDCl_3$) 142.7, 138.1, 138.1, 137.7, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 110.4, 95.7, 80.6, 80.2, 74.7, 73.3, 73.2, 71.2, 69.1; HRMS (ESI): $[M+Na]^+$ found 469.1995. $C_{28}H_{30}O_5Na$ requires 469.1991.

*4.6.4. 3,4,6-Tri-O-benzyl-2-deoxy-2-C-methylene-D-lyxo-hexopyranose **25**.* Compound **25** (0.860 g, 86% yield) was obtained in 4 h as a colourless viscous liquid from the reaction of 3,4,6-tri-*O*-benzyl-2-*C*-hydroxymethyl-D-galactal **23** (1.0 g, 2.24 mmol) with $InCl_3$ (0.099 g, 0.448 mmol). R_f (30% EtOAc/hexane) 0.36. Specific rotation, ^1H and ^{13}C NMR reported here is for an equilibrium mixture of hemiacetal **25** and aldehyde **27** present in a ratio of 1:2. $[\alpha]_D^{28}$ −7.14 (*c* 1.05, $CHCl_3$); ν_{max} (KBr) 3421, 3031, 2920, 2865, 1741, 1688, 1612, 1491, 1455, 1361, 1308, 1217, 1099, 1017, 916, 741, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.58 (1H, s, CHO), 7.38–7.23 (23H, m, aromatic), 6.60 (1H, s, $=CH_2$ of **27**), 6.24 (1H, s, $=CH_2$, of **27**), 5.64 (0.5H, s, $=CH_2$ of **25**), 5.41 (0.5H, s, $=CH_2$ of **25**), 5.27 (0.5H, s, H-1 of **25**), 4.91–4.31 (12H, m), 3.94–3.91 (2H, m), 3.68 (1H, dd, *J*=3.9, 1.8 Hz), 3.58 (1H, dd, *J*=9.6, 6.9 Hz), 3.47 (1H, dd, *J*=9.3, 5.7 Hz), 3.40–3.35 (1H, m), 3.10–3.08 (1H, m).; δ_C (75 MHz, $CDCl_3$) 193.3, 146.8, 141.1, 138.3, 138.2, 137.8, 137.6, 137.2, 135.9, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 127.8, 127.8, 127.7, 127.65, 127.60, 127.5, 127.4, 111.0, 96.0, 78.2, 77.5, 75.6, 75.4, 73.7, 73.2, 73.1, 73.0, 71.9, 71.5, 70.6, 70.4,

69.7, 68.9; HRMS (ESI): $[M+Na]^+$ found 469.1992. $C_{28}H_{30}O_5Na$ requires 469.1991.

4.7. Synthesis of (3*R*,4*S*,5*R*)-3,4,6-tris(benzyloxy)-5-hydroxy-2-hydroxymethylhex-1-ene 32

An equilibrium mixture of compound **25** and **27** (0.210 g, 0.470 mmol) was dissolved in 10 mL of methanol. After 5 min, sodium borohydride (0.027 g, 0.705 mmol) was added slowly to the reaction mixture and the progress of the reaction was monitored by TLC. After 30 min when TLC indicated the completion of the reaction, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with chloroform (3×50 mL). The organic layer was washed with aqueous saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography using hexane/ethyl acetate (4:1) as an eluent to get the diol **32** (0.179 g, 85% yield) as a colourless liquid; R_f (30% EtOAc/hexane) 0.21; $[\alpha]_D^{28}$ −11.6 (*c* 1.00, $CHCl_3$); ν_{max} (KBr) 3432, 3031, 2923, 2865, 1649, 1453, 1389, 1210, 1083, 742, 697, 608 cm^{-1};δ_H (300 MHz, $CDCl_3$) 7.28–7.23 (15H, m, aromatic), 5.36 (1H, s, $=CH_2$), 5.25 (1H, s, $=CH_2$), 4.64–4.45 (5H, m), 4.29 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.14–4.04 (4H, m), 3.74–3.71 (1H, m), 3.52–3.47 (2H m), 2.88 (1H, br s, OH), 2.66 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 145.7, 138.0, 137.8, 137.7, 128.7, 128.6, 128.5, 128.42, 128.45, 128.0, 127.9, 127.86, 127.83, 116.1, 80.5, 79.7, 74.4, 73.4, 70.9, 70.8, 69.7, 63.6; HRMS (ESI): $[M+Na]^+$ found 471.2161. $C_{28}H_{32}O_5Na$ requires 471.2147.

4.8. Synthesis of (3*R*,4*R*,5*R*)-3,4,6-tris(benzyloxy)-5-(methylsulfonyloxy)-2-(methylsulfonyloxymethyl)-hex-1-ene 33

Diol **32** (0.500 g, 1.116 mmol) was dissolved in 10 mL of dry dichloromethane and dried over 4 Å molecular sieves in order to remove any moisture if present. Triethylamine (0.388 mL, 2.79 mmol) was then added and the reaction mixture was cooled to 0 °C. After 5 min, mesyl chloride (0.189 mL, 2.45 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with saturated ammonium chloride solution (20 mL) and extracted with chloroform (3×50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution and then with water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude dimesylate **33** (0.570 g, 85% yield) was obtained as a yellow liquid, which could not be purified by column chromatography due to its instability. R_f (40% EtOAc/hexane) 0.23; ν_{max} (KBr) 3062, 3030, 2870, 1647, 1495, 1454, 1355, 1209, 1174, 1094, 1026, 967, 922, 830, 742, 700, 609 cm^{-1};δ_H (300 MHz, $CDCl_3$) 7.30–7.22 (15H, m, aromatic), 5.38 (1H, s, $=CH_2$), 5.26 (1H, s, $=CH_2$), 4.64 (1H, d, *J*=11.4 Hz, $-OCH_2Ph$), 4.59–4.37 (5H, m), 4.31 (2H, m), 4.15–4.04 (3H, m), 3.89 (3H, s, $-OSO_2CH_3$), 3.75 (1H, dd, *J*=6.3, 3.0 Hz,), 3.50 (1H, d, *J*=5.1 Hz), 2.29 (3H, s, $-OSO_2CH_3$); δ_C (75 MHz, $CDCl_3$) 145.5, 137.8, 137.6, 137.5, 128.38, 128.34, 127.9, 127.8, 127.7, 127.6, 116.2, 80.5, 79.6, 74.4, 73.3, 70.8, 70.7, 69.6, 63.6, 55.3, 36.5; HRMS (ESI): $[M+Na]^+$ found 627.1698. $C_{30}H_{36}O_9S_2Na$ requires 627.1698.

4.9. General procedure for the synthesis of unsaturated azasugars 34–39 and 42

Dimesylate **33** was taken in a flame dried three-necked round bottomed flask and amine (15–20 mL) was added to it. The reaction mixture was stirred at appropriate bath temperature for the corresponding time. The reaction mixture was then quenched with dilute hydrochloric acid and extracted with chloroform (3×50 mL). The combined organic layer was washed with saturated sodium bicarbonate solution, then with water and dried over anhydrous sodium sulfate. The product was purified by column chromatography using hexane/ethyl acetate mixture as an eluent to obtain unsaturated azasugars.

*4.9.1. (2S,3S,4R)-1-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **34**.* Compound **34** (0.334 g, 78% yield) was obtained in 26 h as a colourless low melting solid from the reaction of dimesylate **33** (0.500 g, 0.827 mmol) with 15 mL of benzylamine at 90 °C; R_f (10% EtOAc/hexane) 0.54; $[\alpha]_D^{28}$ −4.5 (*c* 1.10, $CHCl_3$); ν_{max} (KBr) 3030, 2965, 2867, 1653, 1597, 1491, 1452, 1360, 1315, 1236, 1109, 992, 911, 836, 739, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31–7.20 (20H, m, aromatic), 4.98 (1H, s, $=CH_2$), 4.96 (1H, s, $=CH_2$), 4.59 (1H, d, *J*=12.6 Hz, $-OCH_2Ph$), 4.53–4.49 (3H, m), 4.36 (1H, d, *J*=11.7 Hz, $-OCH_2Ph$), 4.29 (1H, d, *J*=12.6 Hz, $-OCH_2Ph$), 4.09 (1H, d, *J*=2.7 Hz), 3.95 (1H, d, *J*=13.5 Hz, $-NCH_2Ph$), 3.86 (1H, dd, *J*=10.5, 2.7 Hz, $-CH_2OBn$), 3.80 (1H, dd, *J*=10.5, 6.0 Hz, $-CH_2OBn$), 3.68 (1H, dd, *J*=9.3, 3.0 Hz, H-3), 3.57 (1H, *J*=13.5 Hz, $-NCH_2Ph$), 3.25–3.21 (1H, m), 3.09 (1H, d, *J*=12.6 Hz, H-6), 2.99 (1H, d, *J*=12.6 Hz, H-6); δ_C (75 MHz, $CDCl_3$) 140.4, 139.3, 138.4, 129.2, 128.35, 128.3, 128.2, 128.0, 127.99, 127.9, 127.6, 127.5, 126.8, 115.0, 76.6, 75.8, 73.3, 71.0, 68.9, 67.9, 60.1, 55.7, 52.7; HRMS (ESI): $[M+H]^+$ found 520.2845. $C_{35}H_{38}NO_3$ requires 520.2852.

*4.9.2. (2S,3S,4R)-1-Propyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **35**.* Compound **35** (0.315 g, 86% yield) was obtained in 28 h as a colourless liquid from the reaction of dimesylate **33** (0.470 g, 0.778 mmol) with 20 mL of propylamine at 60 °C; R_f (10% EtOAc/hexane) 0.38; $[\alpha]_D^{28}$ −2.9 (*c* 0.90, $CHCl_3$); ν_{max} (KBr) 3087, 3063, 3029, 2956, 2926, 2868, 1809, 1725, 1703, 1659, 1605, 1496, 1454, 1361, 1310, 1180, 1099, 1027, 912, 735, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24–7.11 (15H, m, aromatic), 5.01 (1H, s, $=CH_2$), 4.88 (1H, s, $=CH_2$), 4.53 (1H, d, *J*=12.3 Hz, $-OCH_2Ph$), 4.47–4.36 (3H, m), 4.25–4.20 (2H, m), 3.99–3.95 (1H, m), 3.71–3.42 (3H, m), 3.15 (1H, d, *J*=12.3 Hz, H-6), 3.06 (1H, d, *J*=12.0 Hz, H-6), 2.94 (1H, d, *J*=9.6 Hz), 2.58–2. 35 (2H, m), 1.43–1.36 (2H, m), 0.746 (3H, t, *J*=7.5 Hz, $-CH_3$); δ_C (75 MHz, $CDCl_3$) 140.6, 138.3, 128.2, 128.15, 128.11, 128.0, 127.8, 127.5, 127.4, 115.0, 76.7, 75.5, 73.2, 70.9, 68.6, 66.1, 59.1, 53.8, 53.2, 18.3, 11.8; HRMS (ESI): $[M+H]^+$ found 472.2859. $C_{31}H_{38}NO_3$ requires 472.2852.

*4.9.3. (2S,3S,4R)-1-Pentyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **36**.* Compound **36** (0.352 g, 82% yield) was obtained in 22 h as a colourless liquid from the reaction of dimesylate **33** (0.520 g, 0.860 mmol) with 20 mL of pentylamine at 80 °C; R_f (10% EtOAc/hexane) 0.44; $[\alpha]_D^{28}$ −20.0 (*c* 0.30, $CHCl_3$); ν_{max} (KBr) 3063, 3030, 2926, 2861, 1658, 1604, 1493, 1454, 1362, 1322, 1270, 1207, 1098, 911, 737, 606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.27 (15H, m, aromatic), 5.15 (1H, s, $=CH_2$), 5.02 (1H, s, $=CH_2$), 4.67 (1H, d, *J*=12.3 Hz, $-OCH_2Ph$), 4.61–4.50 (3H, m), 4.39–4.34 (2H, m), 4.12 (1H, br m), 3.78–3.59 (3H, m), 3.28 (1H, d, *J*=12.0 Hz, H-6), 3.19 (1H, d, *J*=12.0 Hz, H-6), 3.07 (1H, d, *J*=9.0 Hz), 2.73–2.56 (2H, m), 1.50 (2H, br m), 1.38–1.24 (4H, m), 0.93 (3H, t, *J*=6.6 Hz, $-CH_3$); δ_C (75 MHz, $CDCl_3$) 140.6, 138.2, 128.1, 128.0, 127.9, 127.7, 127.4, 127.3, 114.9, 76.5, 75.4, 73.2, 70.9, 68.6, 66.1, 59.0, 53.1, 51.8, 29.6, 24.6, 22.5, 14.0; HRMS (ESI): $[M+H]^+$ found 500.3164. $C_{33}H_{42}NO_3$ requires 500.3165.

*4.9.4. (2S,3S,4R)-1-Hexyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **37**.* Compound **37** (0.367 g, 77% yield) was obtained in 18 h as a colourless liquid from the reaction of dimesylate **33** (0.560 g, 0.927 mmol) with 20 mL of hexylamine at 90 °C; R_f (10% EtOAc/hexane) 0.57; $[\alpha]_D^{28}$ −22.40 (*c* 0.25, $CHCl_3$); ν_{max} (KBr) 3064, 3030, 2925, 2857, 1726, 1654, 1493, 1455, 1363, 1313, 1105, 911, 737, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.21 (15H, m, aromatic), 5.10 (1H, s, $=CH_2$), 4.96 (1H, s, $=CH_2$), 4.61 (1H, d, *J*=12.6 Hz, $-OCH_2Ph$), 4.52–4.43 (3H, m), 4.30 (2H, d, *J*=13.2 Hz, $-OCH_2Ph$), 4.06 (1H, br m), 3.73–3.60 (3H, m), 3.23 (1H, d, *J*=12.0 Hz, H-6), 3.15 (1H, d, *J*=12.0 Hz, H-6), 3.09 (1H, d, *J*=9.0 Hz),

2.66–2.52 (2H, m), 1.45 (2H, m), 1.25 (6H, m), 0.877 (3H, t, J=6.6 Hz, $-CH_3$); δ_C (75 MHz, $CDCl_3$) 140.4, 138.2, 128.1, 128.07, 128.01, 127.9, 127.7, 127.4, 127.3, 115.1, 76.5, 75.4, 73.1, 70.9, 68.6, 66.1, 59.0, 53.0, 51.8, 31.6, 27.1, 24.8, 22.5, 13.96; HRMS (ESI): $[M+H]^+$ Found 514.3292. $C_{34}H_{44}NO_3$ requires 514.3321.

*4.9.5. (2S,3S,4R)-1-Butyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **38**.* Compound **38** (0.240 g, 71% yield) was obtained in 17 h as a colourless liquid from the reaction of dimesylate **33** (0.420 g, 0.695 mmol) with 20 mL of butylamine at 75 °C; R_f (10% EtOAc/hexane) 0.43; $[\alpha]_D^{28}$ +0.40 (c 1.50, $CHCl_3$); ν_{max} (KBr) 3064, 3030, 2925, 2863, 1657, 1597, 1491, 1455, 1361, 1266, 1207, 1106, 914, 740, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.24 (15H, m, aromatic), 5.15 (1H, s, $=CH_2$), 5.02 (1H, s, $=CH_2$), 4.67 (1H, d, J=12.6 Hz, $-OCH_2Ph$), 4.58–4.49 (3H, m), 4.37 (2H, m), 4.12 (1H, d, J=2.7 Hz), 3.77 (1H, dd, J=10.2, 3.0 Hz), 3.71 (1H, dd, J=11.4, 2.1 Hz), 3.67 (1H, dd, J=9.3, 3.0 Hz), 3.28 (1H, d, J=12.0 Hz, H-6), 3.19 (1H, d, J=12.0 Hz, H-6), 3.06 (1H, d, J=9.3 Hz), 2.79–2.64 (2H, m), 1.52–1.47 (2H, m), 1.35–1.23 (2H, m), 0.94 (3H, t, J=7.2 Hz, $-CH_3$); δ_C (75 MHz, $CDCl_3$) 140.5, 138.25, 138.22, 138.1, 128.14, 128.12, 128.06, 128.03, 127.9, 127.7, 127.4, 127.34, 127.32, 114.9, 76.5, 75.4, 73.1, 70.8, 68.5, 66.0, 59.0, 53.1, 51.5, 27.1, 20.6, 13.9; HRMS (ESI): $[M+H]^+$ found 486.3028. $C_{32}H_{40}NO_3$ requires 486.3008.

*4.9.6. (2S,3S,4R)-1-(2′-Hydroxyethyl)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-C-methylene piperidine **39**.* Compound **39** (0.220 g, 54% yield) was obtained in 22 h as a colourless low melting solid from the reaction of dimesylate **33** (0.520 g, 0.860 mmol) with 20 mL of 2-hydroxyethylamine at 90 °C; R_f (20% EtOAc/hexane) 0.33; $[\alpha]_D^{28}$ −150.8 (c 0.12, $CHCl_3$); ν_{max} (KBr) 3391, 3063, 3029, 2873, 1653, 1603, 1493, 1453, 1394, 1364, 1331, 1279, 1243, 1109, 986, 918, 737, 696, 611 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33–7.19 (15H, m, aromatic), 5.06 (1H, s, $=CH_2$), 5.02 (1H, s, $=CH_2$), 4.63 (1H, d, J=12.6 Hz, $-OCH_2Ph$), 4.50–4.42 (3H, m), 4.33 (1H, d, J=12.3 Hz, $-OCH_2Ph$), 4.30 (1H, J=11.4 Hz, $-OCH_2Ph$), 4.08 (1H, d, J=2.1 Hz), 3.79–3.65 (2H, m), 3.53–3.47 (3H, m), 3.35–3.31 (2H, m), 3.14 (1H, d, J=12.9 Hz, H-6), 2.86–2.78 (1H, m), 2.66–2.59 (1H, m); δ_C (75 MHz, $CDCl_3$) 140.0, 138.10, 138.03, 137.7, 128.28, 128.24, 128.20, 128.0, 127.96, 127.7, 127.6, 127.5, 115.1, 76.3, 75.6, 73.2, 70.7, 68.9, 67.2, 59.3, 59.2, 53.1, 51.1; HRMS (ESI): $[M+H]^+$ found 474.2644. $C_{30}H_{36}NO_4$ requires 474.2644.

4.10. Synthesis of (3*R*,4*R*,5*R*)-3,4,6-tris(benzyloxy)-5-hydroxy-2-hydroxymethylhex-1-ene 40

An equilibrium mixture of compound **24** and **26** (0.250 g, 0.560 mmol) was dissolved in 10 mL of methanol. After 5 min, sodium borohydride (0.032 g, 0.84 mmol) was added slowly to the reaction mixture, and the progress of the reaction was monitored by using TLC. After 30 min when TLC indicated the completion of the reaction, the reaction mixture, was treated with saturated ammonium chloride solution (20 mL) and extracted with chloroform (3×50 mL). The organic layer was washed with saturated bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography using hexane/ethyl acetate (4:1) as an eluent to get the diol **40** (0.210 g, 84% yield) as a colourless liquid; R_f (40% EtOAc/hexane) 0.23; $[\alpha]_D^{28}$ +1.8 (c 0.50, $CHCl_3$); ν_{max} (KBr) 3431, 3030, 2865, 2358, 1642, 1503, 1456, 1358, 1209, 1082, 916, 740, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.22 (15H, m, aromatic), 5.36 (1H, s, $=CH_2$), 5.26 (1H, s, $=CH_2$), 4.66–4.50 (5H, m), 4.32 (1H, d, J=11.4 Hz, $-OCH_2Ph$), 4.18–4.04 (3H, m), 3.98–3.93 (1H, m), 3.75–3.71 (1H, m), 3.66–3.55 (2H, m), 2.82 (1H, br s, 1H, −OH), 2.34 (1H, br s, 1H, −OH); δ_C (75 MHz, $CDCl_3$) 145.5, 137.7, 137.6, 137.4, 128.2, 127.8, 127.7, 127.6, 115.9, 80.3, 79.5, 74.2, 73.2, 70.7, 70.6, 69.4, 63.4; HRMS (ESI): $[M+Na]^+$ found 471.2165. $C_{28}H_{32}O_5Na$ requires 471.2147.

4.11. Synthesis of (3*R*,4*S*,5*R*)-3,4,6-tris(benzyloxy)-5-(methylsulfonyloxy)-2-(methylsulfonyloxymethyl)-hex-1-ene 41

Diol **40** (0.300 g, 0.669 mmol) was dissolved in 10 mL of dry dichloromethane and dried over 4 Å molecular sieves in order to remove any moisture if present. Triethylamine (0.232 mL, 1.67 mmol) was then added and the reaction mixture was cooled to 0 °C. After 5 min, mesyl chloride (0.114 mL, 1.47 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with ammonium chloride solution (20 mL) and extracted with chloroform (3×50 mL). The combined organic layer was washed with saturated solution of sodium bicarbonate solution, water and then dried over anhydrous sodium sulfate, filtered and concentrated. The crude dimesylate **41** (0.356 g, 88% yield) was obtained as a yellow liquid, which could not be purified by column chromatography due to its instability. R_f (40% EtOAc/hexane) 0.25; ν_{max} (KBr) 3028, 2930, 2870, 1457, 1353, 1173, 1096, 924, 824, 745, 701, 526 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.25 (15H, m, aromatic), 5.52 (1H, s, $=CH_2$), 5.34 (1H, s, $=CH_2$), 4.76–4.65 (4H, m), 4.54–4.49 (4H, m), 4.34 (1H, d, J=11.4 Hz, $-OCH_2Ph$), 4.06 (1H, d, J=6.0 Hz), 3.99–3.97 (1H, m), 3.86–3.78 (2H, m), 2.96 (3H, s, $-OSO_2CH_3$), 2.94 (3H, s, $-OSO_2CH_3$); δ_C (75 MHz, $CDCl_3$) 138.8, 137.5, 137.4, 137.3, 128.5, 128.47, 128.40, 128.3, 128.1, 127.9, 127.8, 119.7, 82.3, 81.2, 75.3, 73.3, 71.3, 68.6, 68.3, 38.3, 37.3; HRMS (ESI): $[M+Na]^+$ found 627.1706. $C_{30}H_{36}O_9S_2Na$ requires 627.1698.

4.12. Synthesis of (2*S*,3*R*,4*R*)-1-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-*C*-methylene piperidine 42

Compound **42** (0.127 g, 74% yield) was obtained in 24 h as a colourless liquid from the reaction of dimesylate **41** (0. 200 g, 0.331 mmol) with 20 mL of benzylamine at 90 °C following the general procedure. R_f (10% EtOAc/hexane) 0.45; $[\alpha]_D^{28}$ −6.5 (c 1.10, $CHCl_3$); ν_{max} (KBr) 3031, 2919, 2860, 1650, 1493, 1453, 1361, 1102, 911, 739, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.28 (20H, m, aromatic), 5.25 (1H, s, $=CH_2$), 5.10 (1H, s, $=CH_2$), 4.75 (1H, d, J=12.0 Hz, $-OCH_2Ph$), 4.68 (1H, d, J=12.0 Hz, $-OCH_2Ph$), 4.62–4.51 (4H, m), 4.16 (1H, d, J=5.4 Hz), 3.97–3.77 (5H, m), 3.54–3.51 (1H, m), 3.35–3.25 (2H, m); δ_C (75 MHz, $CDCl_3$) 140.3, 139.5, 138.4, 138.36, 138.30, 128.8, 128.2, 128.19, 128.14, 128.03, 127.60, 127.5, 127.47, 127.41, 127.3, 126.6, 113.8, 79.6, 78.5, 73.0, 72.4, 70.7, 68.3, 59.2, 55.8, 52.3; HRMS (ESI): $[M+H]^+$ found 520.2818. $C_{35}H_{38}NO_3$ requires 520.2852.

4.13. Synthesis of (2*S*,3*S*,4*R*)-1-benzyl-2-(hydroxymethyl)-5-*C*-methylene piperidine-3,4-diol 43

Compound **34** (0.210 g, 0.404 mmol) was dissolved in 10 mL of dry dichloromethane and dried over 4 Å molecular sieves in order to remove any moisture if present. BCl_3 (2.5 mL, 6.0 equiv, 1.0 M solution in heptane) was added to the reaction mixture at 0 °C and the reaction mixture was allowed to stir at room temperature. The reaction was found to be completed in 24 h (monitored by TLC). The reaction mixture was concentrated and the crude product was purified by column chromatography using 10% ammonium hydroxide in methanol as an eluent to obtain compound **43** (0.082 g, 82% yield) as a pale yellow liquid; R_f (10% MeOH/$CHCl_3$) 0.22; $[\alpha]_D^{28}$ −45.2 (c 0.80, MeOH); ν_{max} (KBr) 3398, 3031, 2929, 2851, 1635, 1453, 1405, 1099, 1051, 943, 700, 518 cm^{-1}; δ_H (300 MHz, D_2O) 7.339–7.331 (5H, m, aromatic), 5.25 (1H, s, $=CH_2$), 5.07 (1H, s, $=CH_2$), 4.12 (1H, d, J=6.9 Hz), 3.93–3.84 (5H, m), 3.32–3.22 (3H, m); δ_C (75 MHz, D_2O) 139.1, 134.5, 130.3, 128.8, 128.5, 115.8, 71.9, 70.4, 61.5, 55.8, 50.7; HRMS (ESI): $[M+H]^+$ found 250.1443. $C_{14}H_{20}NO_3$ requires 250.1443.

4.14. Synthesis of (2*S*,3*S*,4*R*)-1-butyl-2-(hydroxymethyl)-5-*C*-methylene piperidine-3,4-diol 44

Compound **38** (0.230 g, 0.474 mmol) was dissolved in 10 mL of dry dichloromethane and dried over 4 Å molecular sieves in order to remove any moisture if present. BCl_3 (2.85 mL, 6.0 equiv, 1.0 M solution in heptane) was added to the reaction mixture at 0 °C and the reaction mixture was allowed to stir at room temperature. The reaction was found to be completed in 24 h (monitored by TLC). The reaction mixture was concentrated. The crude product was purified by column chromatography using 10% ammonium hydroxide in methanol as a eluent to obtain compound **44** (0.093 g, 92% yield) as a pale yellow liquid; R_f (30% MeOH/$CHCl_3$) 0.21; $[\alpha]_D^{28}$ +1.2 (*c* 0.80, MeOH); ν_{max} (KBr) 3414, 2961, 2927, 2855, 1635, 1459, 1405, 1079, 549 cm^{-1}; δ_H (300 MHz, D_2O) 5.40 (1H, s, $=CH_2$), 5.31 (1H, s, $=CH_2$), 4.39 (1H, s), 4.05–3.73 (4H, m), 3.59–3.54 (2H, m), 3.17–3.11 (2H, m), 1.64–1.62 (2H, m), 1.32–1.23 (2H, m), 0.835 (3H, t, *J*=7.2 Hz, $-CH_3$); δ_C (75 MHz, D_2O) δ 135.5, 120.5, 70.3, 66.6, 61.67, 51.7, 25.0, 19.2, 12.8; HRMS (ESI): $[M+H]^+$ found 216.1609. $C_{11}H_{22}NO_3$ requires 216.1600.

4.15. General procedure for inhibition assay

The inhibitory effects of the azasugars were determined spectrophotometrically,[35b] by carrying out the inhibition assay of the glycosidases in the presence of the azasugars as inhibitors utilizing the corresponding *p*-nitrophenyl glycosides as the substrates. α-Glucosidase type I from Baker's yeast, α-galactosidase from green coffee beans, β-galactosidase from *Escherichia coli* and *p*-nitrophenyl-α-D-galactopyranoside were purchased from Sigma Chemicals Co., USA. β-Glucosidase from almond, *p*-nitrophenyl-α-D-glucopyranoside, *p*-nitrophenyl-β-D-glucopyranoside and *p*-nitrophenyl-β-D-galactopyranoside were purchased from SRL Chemicals Ltd., India.

Glycosidase was pre-incubated with various concentrations (0.5–12 mM) of inhibitor for 30 min at its optimum pH and temperature. 20 μL of 25 mM *p*-nitrophenyl glycopyranoside (*p*-NPG) in 0.1 M phosphate buffer was added to the reaction mixture to initiate the reaction. In the case of β-glucosidase acetate buffer was used. The final volume of the reaction mixture was adjusted to 1.1 mL with buffer. Control was also run in parallel without inhibitor. The reaction was then incubated at the same pH and temperature for 10 min and quenched by adding 1 mL of 1 M Na_2CO_3 solution. The glycosidase activity was determined by measuring the *p*-nitrophenol released from *p*-nitrophenyl glycopyranosides at 405 nm using Shimadzu Spectrophotometer UV-1800. IC_{50} value is defined as the concentration of the inhibitor to inhibit 50% of enzyme activity under the assay conditions.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra of compounds **3**, **4**, **12**, **13**, **19a**, **19b**, **24**, **25**, **32**–**44** and ^1H NMR of compound **14**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.050. These data include MOL files and InChIKeys of the most important compounds described in this article.

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