Accepted Manuscript

Design and synthesis of *N*–acetylglucosamine derived 5a-carbasugar analogues as glycosidase inhibitors

Chintam Narayana, Priti Kumari, Daisuke Ide, Nasako Hoshino, Atsushi Kato, Ram Sagar

PII: S0040-4020(18)30223-0

DOI: 10.1016/j.tet.2018.02.063

Reference: TET 29334

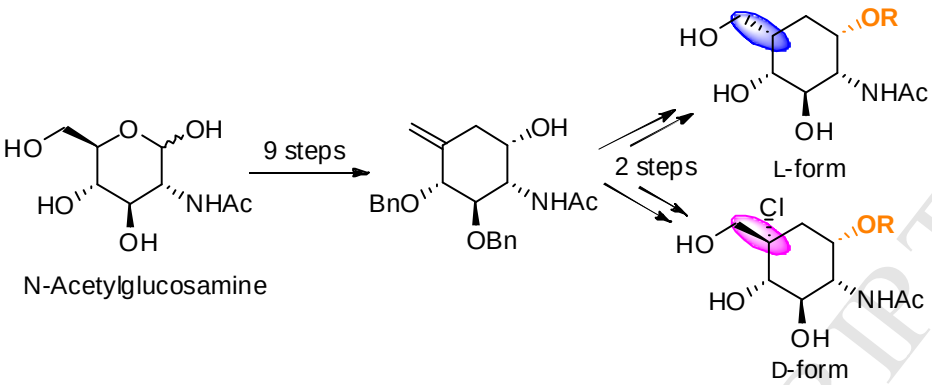
To appear in: *Tetrahedron*

Received Date: 11 October 2017

Revised Date: 16 February 2018

Accepted Date: 27 February 2018

Please cite this article as: Narayana C, Kumari P, Ide D, Hoshino N, Kato A, Sagar R, Design and synthesis of *N*–acetylglucosamine derived 5a-carbasugar analogues as glycosidase inhibitors, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.02.063.



N-Acetylglucosamine

Design and synthesis of *N*–acetylglucosamine derived 5a-carbasugar analogues as glycosidase inhibitors

Chintam Narayana,[1] Priti Kumari,[1] Daisuke Ide,[2] Nasako Hoshino,[2] Atsushi Kato[2] and Ram Sagar[1,3,*]

[1]Department of Chemistry, School of Natural Sciences, Shiv Nadar University (SNU), NH91, Tehsil-Dadri, Gautam Buddha Nagar, Uttar Pradesh, 201314, India.
[2] Department of Hospital Pharmacy, University of Toyama, Sugitani, Toyama 930-0194, Japan.
[3]Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, 221005, India.
[*]E-mail (Corresponding author): ram.sagar@snu.edu.in

ABSTRACT

An efficient synthesis of new six membered carbasugars in both L-form and D-form starting from *N*–acetylglucosamine is described. The key synthetic steps involved regioselective protection and deprotection, Ferrier carbocyclization, Peterson olefination, hydroboration and stereoselective epoxidation followed by regioselective epoxide ring opening reactions. These six member carbasugars showed moderate glycosidase inhibitory activity and one of the compounds was found selective towards β-galactosidase inhibitory activity.

Key words: Carbasugar, Peterson olefination , Glycosidase inhibitors, Ferrier carbocyclization, *N*-acetyl glucosamine.

1. Introduction

Carbasugars are carbohydrate mimics, in which methylene group (-CH_2-) replaces endocyclic oxygen atom.[1] Carbasugars are first prepared by Professor G. E. McCasland and named as pseudosugars.[2] Carbasugars exhibit several biological activities such as antitumor, antiviral, antifungal and as inhibitors/activators of carbohydrate processing enzymes.[3] There are several reports where carbasugars have been used as precursor for synthesizing natural products.[4] Carbasugars are metabolically more stable than their glycopyranoside precursors therefore, they provide better mimics in biological systems.[5] Carbasugars are attractive moieties in drug discovery because of their stability towards endogenous degradative enzymes as well as their interesting biological properties, mainly as antibiotics and as glycosidase inhibitors.[6,7] In fact many carbasugar based drugs have already been developed for therapeutic applications (Figure 1) and they work through inhibiting a particular glycosidase enzyme.[8]

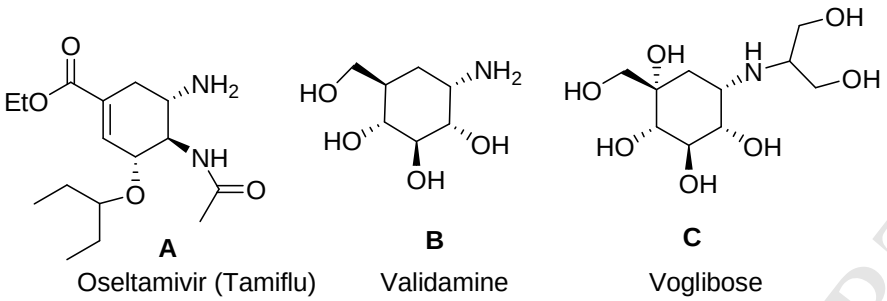


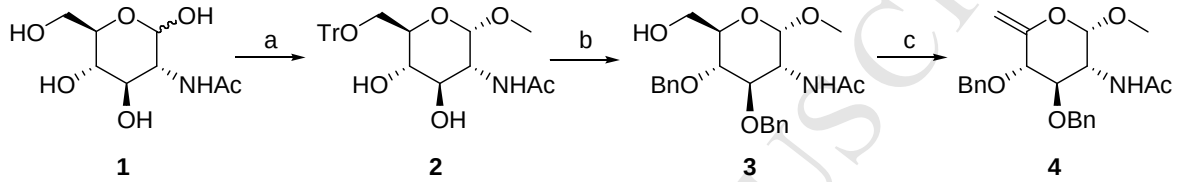
Figure 1. Carbasugar based drug molecules: **A**. Tamiflu, is a currently used antiviral drug; **B**. Validamine, is an antidiabetics drug; **C**. Voglibose, is a drug for diabetes mellitus.

Due to immense biological applications of carbasugars, various research groups devoted significant effort towards synthesis of carbasugar analogues.[1,9] Vankar and coworkers. reported the efficient synthesis of hybrids oxa-carbasugars skelton as glycosidase inhibitors.[10,11] Ramesh and coworkers used a chiron approach for preparing diverse amino cyclitol in the form of carbasugars.[12] Sureshan and coworkers published total synthesis of seven natural carabasugars from vinylogous ketal.[13] Lopez and coworkers used a stereodivergent approach based on 6-endo trig radical cyclization and prepared a number of carbasugars in efficient manner.[14,15] Intramolecular 1,3-dipolar cycloaddition of the sugar derived nitrones were used for the stereoselective synthesis of carbasugars.[16] Pd-catalyzed cyclopropanol ring opening approach has been reported for the synthesis of carbasugar C-1 phosphates.[17] Carbasugars have also been synthesized through Pd-catalyzed cyclitolization /postcyclitolization transformations.[18] Shing and coworkers reported concise and stereodivergent synthesis of carbasugars as SGLT2 inhibitors starting from D-gluconolactone.[19] There are very few reports documented in the literature for the chemical syntheses of *N*-acetylglucosamine based carbasugar derivatives.[20-22] Quiclet-Sire and coworkers used a benzyl carbamate-protected glucosamine derivative as a precursor to a Ferrier carbocyclization followed by a homologation to get carbasugars.[20] Ogawa and coworkers reported a synthesis of the pseudo β-anomer of carba-*N*-acetylglucosamine from noncarbohydrate precursors.[21] Nitz and coworkers reported syntheses of few carbocyclic analogues with one example being *N*-acetylglucosamine carbasugar from methyl D-mannoside.[22]

In view of above reports on the biopotential of carbasugars, we became interested to develop a simple and efficient route for synthesis of new *N*–acetylglucosamine derived carbasugars in both L and D-form that bear a halogen atom at C-5 and different length of alkyl chain at pseudo C-1 position and to study their inhibitory profile with various glycosidase enzymes. Thus in our moderate effort, we have designed and developed efficient synthetic route for the synthesis of new 5a-carbasugars in both L-form and halogenated D-form starting from *N*–acetylglucosamine. These carbasugars were evaluated for their glycosidase inhibitor activity. Herein we are reporting the details of synthetic challenges and successful efficient synthesis along with glycosidase inhibitor activity of thus prepared 5a-carbasugars.

2. Results and Discussion

Synthesis of designed carbasugars was commenced from commercially available *N*–acetyl-D-glucosamine **1** as shown in Scheme 1. *N*–acetyl-D-glucosamine **1** was refluxed with methanol in presence of Amberlite IR-120-H^+ resin to produce methyl glycoside (α:β=9:1) in 90% yield,[23] which upon treatment with tritylchloride in pyridine gave 6-*O*-trityl derivative **2** in good yield.[24] Benzylation on compound **2** followed by removal of trityl group afforded compound **3** with 6-OH as primary alcohol in 80% isolated yield.[25] Tosylation followed by iodination and dehydro-halogenation using NaH in DMF at room temperature furnished olefin compound **4** in very good yield (Scheme 1).

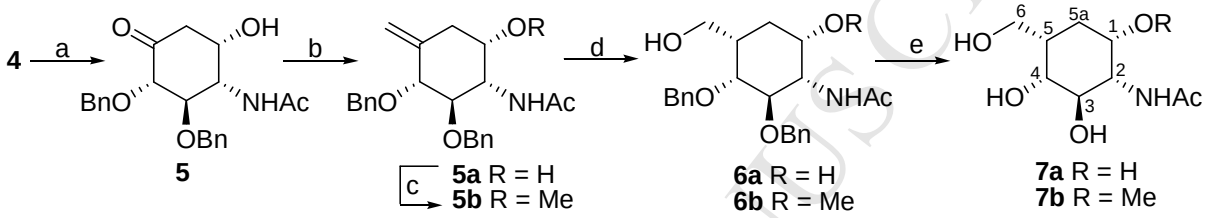


1 **2** **3** **4**

Scheme 1: a) i. Amberlite IR-120 H^+, MeOH, 80 °C, 24 h, 90%; ii. Trityl chloride, pyridine, rt, 48 h, 79%; b) i. NaH, BnBr, THF, 80 °C, rt, 1.5 h; ii. 33% HBr in acetic acid, CH_2Cl_2, 0 °C to rt 80%; c) i. TsCl, Et_3N, CH_2Cl_2, rt, 94%; ii. NaI, DMF 100 °C to rt, NaH, 72%.

Compound **4** was subjected to $HgSO_4$ catalysed Ferrier carbocyclization in 1,4-dioxane and 5 mM H_2SO_4 (2:1) at 50 °C, which cleanly furnish β-hydroxy cyclohexanone **5** as a pure α-isomer with free hydroxyl group at pseudo C-1 position in 65% yield.[26] The next challenging step was to convert this β-hydroxy cyclohexanone **5** into olefin compound **5a**. We attempted several reactions, using phosphine catalysed Wittig reaction,[22] titanium catalysed Petasis reaction[27] and chromium catalysed Takai reaction,[28] to convert β-hydroxy cyclohexanone **5** to β-hydroxy exocyclic olefin **5a** but disappointingly all attempts were unsuccessful. The above reactions either resulted in the formation of undesired aromatic compounds or there was no reaction at all (Table S1, SI). Even protected (OTHP at pesudo C-1) β-hydroxy cyclohexanone failed to give our desired β-hydroxy exocyclic olefin **5a** under Wittig reaction condition. We envisioned that preparing the exocyclic olefin **5a** by dehydrative desilylation in a Peterson olefination[29] condition might be a good alternative to the conventional methods for olefination. This methodology offers many advantages over common protocols for olefination e.g. it would be phosphine free, not involve highly toxic reagents (trimethylsilyl)diazomethane, and involves simpler reaction conditions. Peterson olefination was carried out on β-hydroxyl cyclohexanone **5** which resulted in the formation of the desired product **5a** in acceptable isolated yield (55%) over two steps. At this juncture it was decided to perform stereoselective hydroboration using a bulky hydroboronating reagent, therefore hydroboration reaction was carried out on **5a** using 9-BBN,[22] but surprisingly it didn't work even at elevated temperature. We tried several reaction conditions but none of them resulted in to expected product in good yield (Table S2, SI). At this moment we considered using $BH_3 \cdot THF$[30] as the hydroboronating reagent and indeed it resulted in to expected product and pure product **6a** was obtained after work up and column chromatography

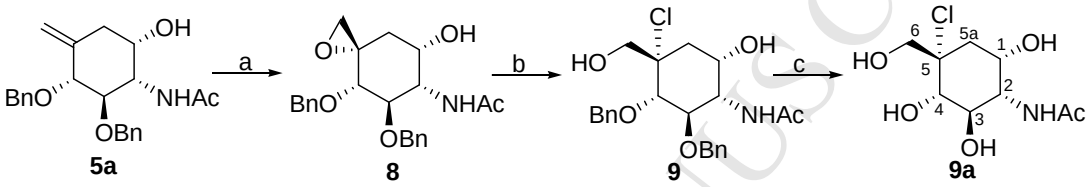
purification. The $BH_3 \cdot THF$ mediated hydroboration was showing more than 95% stereoselectivity towards formation of the L-form of carbasugar **6a** in good yield (65%). In the final step, debenzylation reaction was carried out on **6a** using $Pd(OH)_2$ and hydrogen gas, which furnished the L-form of carbasugar **7a** in 75% yield (Scheme 2). We were interested to see the effect of alkyl substitution at pseudo C-1 in biological activity. Therefore compound **5a** was methylated using methyl iodide in THF, which furnished compound **5b** in very good yield (90%). Hydroboration on **5b** using 9-BBN was again futile, only starting material was recovered; therefore, $BH_3 \cdot THF$ was used as the hydroboration reagent which furnished methylated L-form of carbasugar **6b** in good yield. The debenzylation reaction was done using $Pd(OH)_2$ and H_2 gas, and compound **7b** was obtained in 82% yield (Scheme 2).



Scheme 2: a) $HgSO_4$ 1,4-dioxane:5mM H_2SO_4 (2:1), 50 °C, 3 h, 65%; b) (chloromethyl)trimethyl silane, Mg turnings, THF, rt, then PTSA, CH_2Cl_2, rt 55% in two steps; c) NaH, CH_3I, THF, 0 °C to rt; d) $BH_3 \cdot THF$, H_2O_2, NaOH, THF 0 °C to rt 1.5 h, 65%; e) $Pd(OH)_2$, H_2 gas, methanol, rt, 82%.

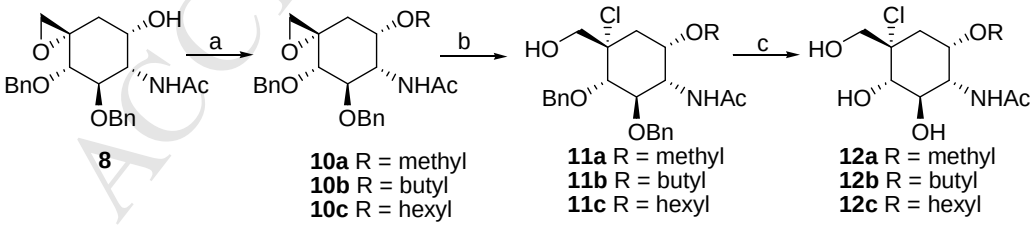
At this juncture we were interested to prepare the D-form of carbasugar **9** in order to compare biological activity with L-form analogues (**7a** and **7b**). We planned to oxidize the primary alcohol in **6b** to get aldehyde, which may easily get recemise to the more stable D-form in presence of pyridine,[22] which followed by reduction and debenzylation may furnish the desired D-form product. Therefore, the compound **6b** was subjected to oxidation with freshly prepared 2-Iodoxybenzoic acid (IBX), but this resulted in a mixture of two products along with undesired α,β-unsaturated aldehyde (Scheme S1, SI) At this juncture, we redesigned our synthetic route and decided to proceed towards stereoselective epoxidation, followed by regioselective epoxide ring opening in order to get our designed final molecules like **9**. Therefore, compound **5b** was subjected to epoxidation using *m*-CPBA in dichloromethane, which showed the formation of two epoxides with desired one in equal ratio (Fig S1, SI). The *m*-CPBA mediated epoxidation reaction on **5a**, having α-pseudo C-1 free hydroxyl group, gave stereoselectively one desired epoxide **8** in very good isolated yield (80%). Here stereoselectivity was controlled by α-pseudo C-1 free hydroxyl group (Fig S2, SI). Boron trifluoride diethyl etherate ($BF_3.Et_2O$) mediated ring opening of epoxide **8** was found inappropriate as it furnished multiple spots on TLC. $TiCl_4$ mediated regioselective ring opening of epoxide on compound **8** gave the desired D-form compound **9** (C-6-β-1° OH) very quickly (5-10 min), confirmed by ^1H NMR, which upon debenzylation furnishes compound **9a** in good yield (Scheme 3). Further stereoselective epoxide ring opening towards the D-form was confirmed by looking at the NH- chemical shift (δ 5.52) in ^1H NMR spectrum of protected derivative **11a** and comparing it with similarly protected intermediate **6b** (L-form,C6-α-1° OH) NH proton chemical shift (δ 6.26). The downfield

chemical shift (NH) in case of L-form (**6b**) was due to hydrogen bonding with C5-CH_2OH (axial), which was not possible when C5-CH_2OH was equatorial, as in the case of compound **11a**. Its worth to mention here that D-form compounds **9a** has a choloro atom installed stereoselectively at C-5 position. The halogenated carbacycles and sugars are known for their better glycosidase inhibitory activity than their nonhalogenated derivatives.[31] We performed preliminary docking studies of compounds **7a**, **9a** and nonhalogenated derivative of **9a** with bovine liver β-galactosidase enzyme and it was found that halogenated derivative **9a** has better binding with β-galactosidase enzyme (SI). The same was noticed experimentally in enzyme binding assays (Table 1).



Scheme 3: a) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 3 h, 80%; b) $TiCl_4$, dry CH_2Cl_2, 0 °C, 10 min, 62%; c) $Pd(OH)_2$, H_2 gas, methanol, rt, 90%.

After getting optimized stereoselective epoxidation reaction condition, it was decided to prepare a different alkyl chain length at α-pseudo C-1 on epoxide **8** through alkylation reaction and study the structure activity relationship in the final compounds. It is evidenced from the literature that, hydrophobicity of the alkyl chain is essential for the cell membrane permeability and enhancement of inhibitory activity.[32] Therefore, epoxide **8** was treated with various alkyl halides in presence of sodium hydride in DMF, which gave corresponding alkyl chain containing derivatives of epoxides **10a**-**10c** in good to very good yield (64-88%). Stereoselective ring opening of epoxides using $TiCl_4$ furnishes desired primary alcohols **11a**-**11c**. The final compounds **12a**-**12c** were obtained after debenzylation reaction using $Pd(OH)_2$ and H_2 gas in methanol at room temperature (Scheme 4).

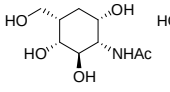
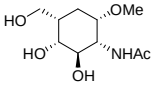
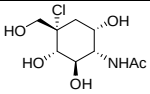
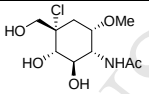
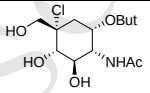
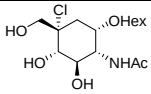


Scheme 4: a) NaH, RBr, DMF, 0 °C to rt, 64-88%; b) $TiCl_4$, CH_2Cl_2, 0 °C, 10 min, 69-72%; c) $Pd(OH)_2$, H_2 gas, methanol, rt, 77-83%.

Glycosidase inhibition activity of all the final prepared compounds were carried out using various glycosidase enzymes and adopting standard enzyme assays protocol,[33] the results are summarized

in Table 1. Compound **7a**, **7b** and **9a** did not show any significant inhibition toward all glycosidases. In contrast, compound **12a** with *O*-Me group in the α-pseudo C-1 position showed selective inhibition activity against bovine liver β-galactosidase, with IC_{50} 0.77 mM. Furthermore, this study revealed that extension of *O*-alkyl group tends to increase their inhibitions. Compound **12b** with *O*-butyl group in the α-pseudo C-1 position showed inhibition activity against β-glucosidase, bovine liver and β-galctosidase, bovine liver with IC_{50} 1.70 and 1.0 mM, respectively. Compound **12c** showed inhibition toward yeast α-glucosidase, bovine liver β-glucosidase, bovine liver β-galactosidase, coffee beans α-glucosidase, bovine kidney α-L-fucosidase, and *E. coli* β-glucuronidase, with IC_{50} 0.32, 0.40, 0.25, 0.19, 0.42, and 0.17, respectively.

Table 1. Glycosidase inhibition activity

compounds / enzymes	 **7a**	 **7b**	 **9a**	 **12a**	 **12b**	 **12c**
α-glucosidase yeast	NI[a] (1.8%)[b]	NI (11.0%)	NI (2.6%)	NI (1.8%)	NI (11.8%)	**0.32**[c]
β-glucosidase bovine liver	NI (16.1%)	NI (22.4%)	NI (19.3%)	NI (27.1%)	**1.7**	**0.40**
β-galctosidase bovine liver	NI (18.9%)	NI (16.8%)	NI (10.0%)	**0.77**	**1.0**	**0.25**
α-galctosidase coffee beans	NI (0.0%)	NI (0.0%)	NI (0.0%)	NI (0.0%)	NI (0.0%)	**0.19**
α-mannosidase jack bean	NI (0.0%)	NI (0.6%)	NI (0.0%)	NI (0.0%)	NI (0.3%)	NI (20.6%)
β-mannosidase snail	NI (0.0%)	NI (0.3%)	NI (0.0%)	NI (0.0%)	NI (0.0%)	NI (9.4%)
α-L-fucosidase bovine kidney	NI (3.9%)	NI (5.9%)	NI (1.0%)	NI (0.0%)	NI (2.5%)	**0.42**
β-glucuronidase E-coli	NI (4.5%)	NI (2.9%)	NI (15.1%)	NI (11.1%)	NI (23.4%)	**0.17**

[a]NI- No inhibition (less than 50% inhibition at 1 mM concentration), [b]( )-actual inhibition % at 1 mM, [c]IC50 (50% inhibition, concentration in mM)

3. Conclusions

In summary, we have developed an efficient synthetic protocol for the synthesis of new *N*–acetyl glucosamine derived carbasugars in both L- and D-forms in good to very good yield. We have shown that the Peterson olefination is key reaction condition for doing olefination on the β-hydroxy ketone system, where other olefination reactions unsuccessful due to high reactivity of this substrate towards elimination reaction and aromatization. These carbasugar molecules were designed based on literature reports on bio-potentials of this class of molecules. Subsequently, we have successfully demonstrated that these synthesized carbasugars possess moderate glycosidase inhibitor activity, and one of the carbasugar is very selective towards β-galactosidase enzymes. This selective inhibition activity opens a new door for making more derivatives of

these analogues and to study the mechanism of its inhibition. The complete library realization of this new carbasugar and their enzyme inhibition activity will be reported in due course of time.

4. Experimental

4.1. General Experimental Methods.

All experiments were performed in an oven-dried apparatus and using anhydrous solvents. High-resolution ESI mass spectra were recorded using Agilent 6540 Q-TOF instrument. Optical rotations were measured on krüss polarimeter. Solvents were distilled using standard distillation procedure and stored on 4Å molecular sieves. ^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectra were recorded with a Bruker AMX-400 MHz instrument. ^{1}H and ^{13}C chemical shifts are referenced to the solvents residual signals ($CDCl_3$: δ 7.26 in ^{1}H NMR and δ 77.16 in ^{13}C NMR; CD_3OD: δ 3.31 in ^{1}H NMR and δ 49.00 in ^{13}C NMR) and reported in parts per million (ppm) at 25 °C. Coupling constants are expressed in hertz (Hz). Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254), Spots were visualized by phosphomolybdic acid and 10% H_2SO_4 in ethanol.

*4.2.Methyl 6-O-trityl 2-deoxy-2-acetamido-α-D-glucopyranoside (**2**).*

Amberlite IR 120 H^+ resin (20 g) was added to a pre-stirred solution of *N*-Acetyl D-glucosamine (20 g, 90.41 mmol) in methanol (200 mL). Reaction mixture was stirred at 80 °C for 24 h or until it becomes clear solution. Reaction mixture was cooled to room temperature and filtered through sintered funnel, filtrate was concentrated and evaporated to dryness to obtain compound methyl *N*-acetyl-D-glucosamine as white solid (20 g, 90%). as anomeric mixture (α:β, 9:1), which was used in next step without any further purification. To a stirred solution of methyl *N*-acetyl-D-glucosamine (15.2 g, 64.68 mmol) in anhydrous pyridine, Trityl chloride (21.63 g, 77.61 mmol) and DMAP (0.7 g, 6.46 mmol) were added and the resulting mixture was stirred at room temperature for 48 h. After completion of the reaction (TLC), the reaction mixture was diluted with water (150 mL) and extracted with ethyl acetate (3 × 150 mL), the combined organic layer was washed with copper sulfate solution (250 mL) followed by saturated brine solution (200 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get the residue. The residue was purified by column chromatography (ethyl acetate/methanol: 95:5) to furnish compound **2** as an amorphous solid (24.5 g) in 79% isolated yield.

$[\alpha]_D^{20}$ +28.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.21 (m,15H), 5.91 (d, *J* = 8.4 Hz, 1H, NH), 4.70 (d, *J* = 4.0 Hz, 1H, H-1), 4.08 (ddd, *J* = 10.0 Hz, 8.8 Hz, 3.6 Hz, 1H, H-2), 3.67-3.59 (m, 2H, H-5 and H-3), 3.54 (t, *J* = 8.0 Hz, 1H, H-4), 3.43 (dd, *J* = 2.8 Hz, 6.4 Hz, 1H, H-6a), 3.40 (s, 3H, OCH_3), 3.34 (dd, *J* = 5.6 Hz, 10.0 Hz, 1H, H-6b), 2.04 (s, 3H, NH*Ac*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (NH*CO*), 143.9 (ArqC), 128.8, 128.1, 128.0, 127.2 (ArC), 98.2 (C-1), 87.0 (*C*Ph_3), 74.4 (C-3), 72.8 (C-4), 70.2 (C-5), 63.9 (C-6), 55.1 (O*C*H_3), 53.8 (C-2), 23.4 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{28}H_{31}NO_6$ $[M+Na]^+$ 500.2044, found 500.2063.

*4.3. Methyl 3,4-di-O-benzyl-2-deoxy-2-acetamido-α-D-glucopyranoside (**3**).*

To a stirred solution of compound **2** (14 g, 29.32 mmol) in anhydrous THF, sodium hydride (3.5 g, 87.96 mmol, 3.0 equiv) was added at 0 °C. After 20 min, benzyl bromide (10.4 mL, 87.96 mmol, 3.0 equiv) was added drop wise and the resulting mixture was heated at 80 °C with stirring for 1.5 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool down to room temperature and then it was quenched by adding methanol (10 mL). The reaction mixture was dissolved in ethyl acetate (500 mL) and washed with water (3 × 200 mL) followed by saturated brine solution (2 × 250 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to get a yellow residue. The residue was washed with pentane to furnish corresponding benzylated derivative of compound **2** as a brown sticky solid (15 g, 78%), which was used in the next step without further purification. To a solution of benzylated derivative of compound **2** (10 g, 15.28 mmol) in anhydrous CH_2Cl_2, a 33% solution of HBr in acetic acid (6.6 mL) was added at 0 °C drop wise. The reaction mixture was stirred for 10 min at same temperature. Completion of the reaction was confirmed by TLC, after the reaction mixture was quenched with ice cold water (50 mL) and extracted with CH_2Cl_2 (400 mL) the combined organic layer washed with water (100 mL), saturated sodium bicarbonate solution (250 mL) and saturated brine solution (100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure which gave a residue. The residue was purified by flash column chromatography (ethylacetate/hexane 80: 20) which gave compound **3** as white gelatinous solid, which after re-crystallization with CH_2Cl_2 furnished the title compound **3** as a white solid (5 g) in 80% isolated yield. $[\alpha]_D^{20}$ +42.5 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 8.0 Hz, 1H, N-H), 7.35–7.23 (m, 10H, ArH), 4.77 (t, *J* = 6.4 Hz, 1H, O-H), 4.73-4.60 (m, 4H, 2 × CH_2Ph), 4.54 (d, *J* = 3.6 Hz, 1H, H-1), 3.96 (ddd, *J*

= 12.8 Hz, 10.4 Hz, 3.2 Hz, 1H, H-2), 3.71 (dd, *J* = 8.4 Hz, 4.0 Hz, 1H, H-3), 3.66 (dd, *J* = 4.0 Hz, 11.6 Hz, 1H, H-6a), 3.59-3.56 (m, 1H, H-6b), 3.51-3.47 (m, 2H, H-4, H-5), 3.30 (s, 3H, OCH_3), 1.85 (s, 3H, NH*Ac*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3 (NH*CO*), 138.7, 138.4 (ArqC), 128.2, 128.1, 127.6, 127.5, 127.4, 127.3 (ArC), 98.2 (C-1), 79.9, 78.0 (C-3, C-4), 74.0, 73.9 (*C*H_2Ph), 71.69 (C-5), 60.1 (C-6), 54.3 (O*C*H_3), 52.6 (C-2), 22.5 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{29}NO_6$ $[M+Na]^+$ 438.1887, found 438.1910.

*4.4. Methyl 3,4 -di-O-benzyl-2,6-di-deoxy-2-acetamido-α-D-xylohex-5-enoside (**4**).*

To a stirred solution of compound **3** (7.0 g, 16.86 mmol) in anhydrous CH_2Cl_2, was added DMAP (0.206 g, 1.686 mmol) and triethyl amine (23 mL, 168.6 mmol). The reaction mixture was cooled to 0 °C and tosyl chloride (3.5 g, 18.54 mmol) was added portion wise over 30 min and resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to rt and stirred for another 12 h. After completion of the reaction (TLC), the reaction mixture was quenched with saturated ammonium chloride solution (100 mL) and extracted with CH_2Cl_2 (5 × 50 mL), the combined organic layer was washed with brine solution (100 mL) dried over Na_2SO_4, filtered and evaporated to get sticky residue. The residue was purified by column chromatography over silica gel (hexane/ethyl acetate 30:70) to furnish corresponding tosylated derivative of **3** (9.0 g) in 94% isolated yield.

To a stirred solution of tosylated derivative of **3** (8.0 g, 14.05 mmol) in anhydrous DMF, Sodium iodide (21.06 g, 140.54 mmol, 10 equiv) was added. The reaction mixture was stirred at 80 °C for 3 h. After completion of reaction (TLC), reaction mixture was cooled to room temperature and sodium hydride (1.12 g, 28.1 mmol) was added portion wise to this mixture. The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 150 mL) the combined organic layer was washed with brine solution, dried over Na_2SO_4, filtered and evaporated to dryness to obtain crude residue. The residue was purified by flash column chromatography (ethylacetate/ hexane 1:1 to pure ethyl acetate), to furnish compound **4** as a white color solid (4.0 g) in 72% isolated yield. $[\alpha]_D^{20}$ +57.5 (*c* 0.2, MeOH): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, ArH, 10H), 5.42 (d, *J* = 9.2 Hz, 1H, NH), 4.83 (d, *J* = 11.6 Hz, 2H, C*H*$_2$Ph), 4.79-4.69 (m, 4H), 4.32 (dt, *J* = 3.2 Hz and 9.2 Hz ,1H, H-2), 4.01 (d, *J* = 8.0 Hz, 1H, H-4), 3.63 (t, *J* = 9.2 Hz, 1H, H-3), 3.39 (s, 3H, OCH_3), 1.84 (s, 3H, NH*Ac*); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 169.9 (NHCO), 153.8, 138.4, 137.8 (ArqC), 128.62, 128.6, 128.3, 128.0, 127.9 (ArC), 99.6 (C-1), 97.7 (C-6), 79.7 (C-2), 78.6 (C-3), 74.5, 73.9 (2 × *C*H_2Ph), 55.7 (OCH_3), 51.8 (C-4), 23.5 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{27}NO_5$ $[M+H]^+$ 398.1962, found 398.1991.

*4.5. Synthesis of compound (**5**).*

To a solution of compound **4** (4.0 g, 10.07 mmol) in 1,4-dioxane and 5mM H_2SO_4 (2:1, 120 mL) was added $HgSO_4$ (0.746 g, 2.51 mmol). The reaction mixture was stirred at 50 °C for 3 h. After completion of reaction (TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine solution, dried over sodium sulphate, filtered and evaporated to give a crude compound. The residue was washed with diethyl ether, to furnish corresponding ketone compound **5** as a white color powder (2.5 g, 65%). $[\alpha]_D^{20}$ +12.5 (*c* 0.2, MeOH): ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, *J* = 9 Hz, 1H. NH), 7.38-7.22 (m, 10H), 5.41 (d, *J* = 3.6 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H, C*H*$_2$Ph), 4.71 (d, *J* = 11.0 Hz, 1H, C*H*$_2$Ph), 4.61 (d, *J* = 11.0 Hz, 1H, C*H*$_2$Ph), 4.45 (d, *J* = 11.6 Hz, 1H, C*H*$_2$Ph), 4.35 (d, *J* = 9.4 Hz, 1H, H-4), 4.30 (td, *J* = 2.0 Hz and *J* = 10.8 Hz, 1H, H-2), 3.93 (quint, *J* = 2.8 Hz, 1H, H-3), 3.74 (t, *J* = 9.6 Hz, 1H, H-3), 2.89 (dd, *J* = 14.0 Hz and 2.4 Hz, 1H, H-5a), 2.30 (dd, *J* = 13.6 Hz and 3.2 Hz, H-5a'), 1.84 (s, 3H, NH*Ac*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 205.5 (*C*=*O*), 169.1 (NH*C*=O), 138.9, 138.5 (ArqC), 128.1, 128.0, 127.6, 127.5, 127.4, 127.2 (ArC), 86.1 (C-4), 80.0 (C-3), 73.7, 72.3 (2 × CH_2Ph), 67.1 (C-1), 53.6 (C-2), 45.7 (C-5a), 22.7 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{22}H_{25}NO_5$ $[M+H]^+$ 384.1805, found 384.1826.

*4.6. 2-Acetamido-3,4-di-O-benzyl-6-deoxy -5a -Carba-α-D-xylo-hex-5-enopyranose (**5a**).*

To a round bottom flask Magnesium turnings (1.5 g, 65.25 mmol) and Iodine (catalytic) were added under argon atmosphere. The flask was heated (50-60 °C) with hot gun for 5 min then cooled to rt. Anhydrous THF (5 ml) was added followed by addition of (chloromethyl) trimethylsilane (2 mL). The reaction mixture was again heated with hot gun in order to initiate reaction followed by addition of remaining (chloromethyl) trimethylsilane (6.4 g, 52.2 mmol) and THF (35 mL) at rt. The resulting mixture was stirred at room temperature for 1 h. Compound **5** (1.0 g, 2.61 mmol) in anhydrous THF (15 mL) was added to this mixture and stirring was continued for another 1 h. After completion of reaction (confirmed by TLC) the reaction mixture was quenched with methanol (10 mL), diluted with saturated NH_4Cl solution (50 mL) and

extracted with dichloromethane (3 × 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over sodium sulphate, filtered and evaporated to get silylated Grignard product derivative, which was forwarded next step without further purification. To a stirred solution of Grignard product derivative (1.2 g, 5.21mmol) in anhydrous CH_2Cl_2 was added *p*-toluenesulfonic acid monohydrate (0.44g, 2.60 mmol) portion wise. The reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (TLC), the reaction mixture was quenched with triethyl amine evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over sodium sulphate, filtered and evaporated to dryness obtained a crude product residue. The crude product residue was purified by column chromatography (Ethyl acetate: hexane, 8:2) to furnished compound **5a** as an off-white solid (0.54 g) in 55% isolated yield over two steps: $[\alpha]_D^{20}$ +46.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 10H), 6.78 (brs, NH), 5.23 (s, 1H, =CH), 5.17 (s, 1H, =CH), 4.63 (s, 2H), 4.59 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.44 (quin, *J* = 4.0 Hz, 1H, H-2), 4.34 (d, *J* = 10.0 Hz, 1H, C*H*$_2$Ph), 4.09 (quin, *J* = 4.5 Hz, 1H, H-1), 3.95 (d, *J* = 5.0 Hz, 1H, H-4), 3.65 (t, *J* = 5.0 Hz, 1H, H-3), 2.98 (brs, 1H), 2.41 (dd, *J* = 8.0 Hz, 4.9 Hz, 2H, H-5a and H-5a'), 1.84 (s, 3H, NH*Ac*); ^{13}CNMR (100 MHz, $CDCl_3$) δ 172.0 (NH*C*O), 140.4, 137.9, 137.7 (ArqC), 128.7, 128.6, 128.2, 128.0, 127.9, 127.8 (ArC), 117.1 (=CH_2), 81.2 (C-3), 78.3 (C-4), 72.4, 70.8 (2 × CH_2Ph), 69.5 (C-1), 52.6 (C-2), 35.0 (C-5a), 23.4 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{27}NO_4$ $[M+H]^+$ 382.2013, found 382.2042.

*4.7. Methyl 2-acetamido-3,4-di-O-benzyl-6-deoxy -5a -Carba-α-D-xylo-hex-5-enopyranoside (**5b**).*

To a stirred solution of sodium hydride (0.3 g, 0.789 mmol) in anhydrous THF (3 mL) at 0 °C was added a solution of compound **5a** (0.047 g, 1.18 mmol) in anhydrous THF (2 mL) dropwise and resulting reaction mixture was stirred at 0 °C for 10 min. Methyl iodide (0.24 mL, 3.945 mmol) was added dropwise to this reaction mixture and stirring was continued at room temperature for 3 h. After completion (TLC) of reaction, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (25 mL) and extracted with ethyl acetate (2 × 25 mL). The organic phase was separated; aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were washed with saturated brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by

column chromatography (Ethyl acetate/hexane 6:4) to furnish compound **5b** as a colourless solid (0.280 g) in 90% isolated yield. $[\alpha]_D^{20}$ +42 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H, ArH), 6.14 (bs, 1H), 5.19 (s, 1H, =C-H), 5.11 (s, 1H, =C-H), 4.73 (d, *J* = 9.6 Hz, 1H, CH_2Ph), 4.59 (d, *J* = 10.0 Hz, 2H, CH_2Ph), 4.50-4.44 (m, 2H), 3.95 (d, *J* = 5.0 Hz, 1H, H-2), 3.62 (t, *J* = 5.0 Hz, 1H, H-3), 3.54-3.51 (m, 1H, H-1), 3.32 (s, 3H, OMe), 2.50 (dd, *J* = 6.4 Hz and 11.2 Hz, 1H, H-5a), 2.26 (dd, *J* = 2.4 Hz and 11.2 Hz, H-5b), 1.82 (s, 3H, $COCH_3$); ^{13}CNMR (125 MHz, $CDCl_3$) δ 169.7 (NH*C*O), 140.5, 138.2, 137.9 (ArqC), 128.4, 128.3, 127.9, 127.8, 127.6 (ArC), 114.2(=C), 82.2 (C-3), 79.7 (C-4), 77.08 (C-1), 73.3, 71.6 (2 × CH_2Ph), 56.3 (O*C*H_3) , 50.1 (C-2), 32.7 (C-5a), 23.5 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{24}H_{29}NO_4$ $[M+H]^+$ 396.2169, found 396.2137.

4.8.General Procedure for the preparation of carbasugars 6a-b and 7a-b

*4.8.1. 2-Acetamido-2-deoxy-3,4-di-O-benzyl-5a-carba-α-L-Iodopyranose (**6a**).* To a stirred solution of compound **5a** (0.4 g, 1.05 mmol) in anhydrous THF under nitrogen atmosphere was added BH_3·THF (3.1 mL, 3.14 mmol, 1M in THF) dropwise at 0 ℃. The resulting solution was stirred at room temperature (rt) till disappearance (TLC) of the starting material (1.5 h). 3M NaOH (1 mL) solution and 30% H_2O_2 solution (1.5 mL) was added to the reaction mixture at 0 °C and resulting mixture was stirred for 1h at rt. The reaction mixture was quenched with 0.5 N $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography (Ethyl acetate) to furnish the desired carbasugar derivative **6a** as colorless oil (0.27 g, 65%). $[\alpha]_D^{20}$ +15.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.38-7.27 (m, 10H, ArH), 6.83 (brs, 1H, NH), 4.67 (d, *J* = 9.6 Hz, 1H, C*H*$_2$Ph), 4.57-4.47 (m, 4H, C*H*$_2$Ph and H-2), 4.12 (dt, *J* = 3.6 and 9.2 Hz, 1H, H-1), 3.81 (m, 1H, H-4), 3.74 (t, *J* = 2.8 Hz, 1H, H-3), 3.68-3.66 (m, 2H, H-6), 2.12-2.10 (m, 1H, H-5), 1.78 (s, 3H, NH*Ac*), 1.64 (td, *J* = 3.6 Hz and 10.4 HZ, 1H, H-5a), 1.50 (dd, *J* = 9.6Hz and 19.2 Hz 1H, H-5a'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (NH*CO*), 137.7, 137.4 (ArqC), 128.8, 128.5, 128.5, 128.1, 128.0, 127.7 (ArC), 76.8 (C-4), 75.2 (C-3), 73.4(CH_2Ph), 72.1 (CH_2Ph), 68.0 (C-1), 63.5 (C-6), 51.6 (C-2), 37.9 (C-5), 25.6 (C-5a), 23.3 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{29}NO_5$ $[M+H]^+$ 400.2118, found 400.2125.

*4.8.2. Methyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-5a-carba-α-L-Iodopyranoside (**6b**).* To a stirred solution of compound **5b** (0.209 g, 0.50 mmol) in anhydrous THF was added BH_3·THF (1.01 ml, 1M in THF, 1.01 mmol), dropwise at 0 °C. The resulting solution was stirred at room temperature for 2.5 h. TLC (Ethyl acetate) showed that the starting material was consumed completely. 3N NaOH aqueous solution (1.0 mL, 3.03 mmol) and 30% H_2O_2 solution (1 mL) was added at 0 °C and reaction mixture was stirred for another 2 h at room temperature. The reaction mixture was quenched with 0.5 N $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography (Ethyl acetate/hexane 8:2) to give compound **6b** as a colourless oil. (0.132 g), 61% isolated yield. $[\alpha]_D^{20}$ +17.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 8H, ArH), 7.26-7.23 (m, 2H, ArH), 6.27 (d, *J* = 9.2 Hz, 1H, NH), 4.74 (dd, *J* = 4.4 Hz, 1H, H-2), 4.69 (d, *J* = 11.9 Hz, 1H, C*H*$_2$Ph), 4.57 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.49 (dd**,** *J* = 11.2 Hz, 2H, CH_2Ph), 3.87 (t, *J* = 8.0 and 10.4 Hz, 1H, H-3), 3.77 (t, *J* = 2.4 Hz, 1H, H-4), 3.71 (brd, *J* = 7.6 Hz, 1H, H-6a), 3.64 (dd, *J* = 4.8 Hz, 10.4 Hz, 1H, H-6b), 3.58 (dt, *J* = 4.4 and 11.6 Hz, 1H, H-1), 3.32 (s, 3H, OCH_3), 2.16-2.12 (m, 1H, H-5a), 1.78 (s, 3H, NH*Ac*), 1.65 (dt, *J* = 4.4 and 13.2 Hz, H-5), 1.53 (brd, *J* = 12.4 Hz, H-5a'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (NHCO), 138.0, 137.4 (ArqC), 128.8, 128.6, 128.4, 128.1, 127.9, 127.8 (ArC), 75.6, 74.9, 72.7, 72.4, 64.2, 56.6 (OCH_3), 38.1, 25.0 (C-5a), 23.5 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{24}H_{31}NO_5$ $[M+H]^+$ 414.2275, found 414.2263.

*4.9. Synthesis of compound **7a** and **7b**.* To a solution of compound **6a** (0.12 g, 3.03 mmol) in methanol was added $Pd(OH)_2$/C (20 mg, 20 wt % on carbon, wet) at room temperature. The reaction mixture was stirred under H_2 gas (balloon) for 12 h. The reaction mixture was filtered through celite, and the filtrate was evaporated to dryness to furnish compound **7a** (49 mg, 75%) as a colorless sticky solid. Similarly compound **7b** (32 mg, 82%) was prepared starting from **6b** (70 mg, 0.16 mmol).

*4.9.1. 2-Acetamido-2-deoxy-5a-carba-α-L-Iodopyranose (**7a**).* $[\alpha]_D^{20}$ +11.3 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, D_2O): δ 4.08-4.05 (m, 2H), 3.93-3.88 (m, 2H), 3.76-3.74 (m, 2H), 2.21-2.17 (m, 1H, H-5a), 2.06 (s, 3H, NH*Ac*), 1.77 (m, 2H, H-5a', H-5); ^{13}C NMR (100 MHz, D_2O): δ 174.1 (NH*C*O), 71.2, 70.3, 66.8, 62.1 (C-1, C-3, C-4, and C-7) 54.4 (C-2), 38.4 (C-5), 29.8 (C-6), 22.2 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_9H_{17}NO_5$ $[M+Na]^+$ 220.1179, found 220.1172.

*4.9.2. Methyl 2-acetamido-2-deoxy-5a-carba-α-L-Iodopyranoside (**7b**).* $[\alpha]_D^{20}$ +12.6 (*c* 0.5, CH_3OH); ^1H NMR (400 MHz, D_2O) δ 4.22 (brs, 1H), 3.89 (s, 2H), 3.78 (dd, *J* = 7.2 and 11.2 Hz, 1H), 3.71-3.64 (m, 2H), 3.36 (s, 3H, OCH_3), 2.18 (m, 1H, H-5a), 2.04 (s, 3H, NH*Ac*), 1.72-1.68 (m, 2H, H-5a' & H-5); ^{13}CNMR (100 MHz, D_2O) δ 173.9 (NHCO), 76.5 (C-3), 70.5 (C-4), 62.2 (C-6), 56.2 (OCH_3), 51.6 (C-1), 48.8 (C-2), 38.3 (C-5), 23.9 (C-5a), 22.2 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{10}H_{19}NO_5$ $[M+Na]^+$ 256.1155, found 256.1172.

*4.10. Synthesis of compound (**8**).*

To a solution of compound **5a** (0.250 g, 0.45 mmol) in anhydrous CH_2Cl_2 was added *m*-CPBA (0.22 g, 1.31 mmol) and suspension was stirred at rt for 3 h. After completion (TLC) of reaction, the reaction mixture was quenched with sodium bicarbonate solution (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine solution (50 mL) dried over Na_2SO_4 filtered and evaporated to dryness to obtain a crude compound. The residue was purified by flash chromatography (Ethyl acetate), to furnished compound **8** as a white color solid (0.208 g, 80%). $[\alpha]_D^{20}$ +19.3 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 10H, ArH), 6.88 (brs, 1H), 4.87 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.63 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.54 (d, *J* = 12.4 Hz, 3H, CH_2Ph), 4.24 (dt, *J* = 4.0 Hz and *J* = 10.4 Hz, 1H, H-2), 3.75 (t, *J* = 4.0 Hz, 1H, H-3), 3.35 (d, *J* = 3.2 Hz, 1H, H-4), 2.68 (s, 2H, H-6), 2.26 (t, *J* = 11.6 Hz, 1H, H-5a), 1.84 (s, 3H, NH*Ac*), 1.54 (d, *J* = 10.8 Hz, 1H, H-5a'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (NH*CO*), 137.6, 137.5 (ArqC), 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.6 (ArC), 80.2, 77.8, 77.3, 73.2, 72.7, 69.0, 57.3, 51.7, 50.5, 32.8, 23.3 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{27}NO_5$ $[M+Na]^+$ 420.1781, found 420.1829.

*4.11. 2-Acetamido-2-deoxy-3,4-di-O-benzyl-5-chloro 5a-carba-α-D-glucopyranose (**9**).*

To a stirred solution of compound **8** (0.03 g, 0.07 mmol) in anhydrous CH_2Cl_2 at 0 °C, $TiCl_4$ (0.18 ml, 1M in CH_2Cl_2, 0.15 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 minutes. TLC (Ethylacetate : hexane, 9:1) showed that starting material was consumed. The reaction was quenched with sodium chloride solution (5 mL) and extracted with CH_2Cl_2 (2 × 20 mL), The combined organic layer was washed with brine solution dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography

(Ethyl acetate/hexane,7:3), to furnish compound **9** as a colorless oil (0.020 g, 62%): $[\alpha]_D^{20}$ +21.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 10H, ArH), 5.89 (d, *J* = 8.0 Hz, 1H, NH), 4.98 (d, *J* = 10.4 Hz, 1H, CH_2Ph), 4.83 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.69 (d, *J* = 10.8 Hz, 2H, CH_2Ph), 4.09 (t, *J* = 8.0 Hz, 1H, H-2), 3.95-3.82 (m, 4H), 3.53 (d, *J* = 10.8 Hz, 1H, H-6a), 3.34 (d, *J* = 10.8 Hz, 1H, H-6b), 3.24 (s, 1H), 2.03 (brs, 2H, H-5a), 1.84 (s, 3H, NH*Ac*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (NHCO), 138.1, 137.6 (ArqC), 128.75, 128.7, 128.4, 128.3, 128.0 (ArC), 80.9 (C-3), 79.2 (C-4), 77.8 (C-5), 76.0 (CH_2Ph), 75.6 (CH_2Ph), 69.8 (C-1), 54.7 (C-2), 47.5 (C-6), 34.6 (C-5a), 23.6 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{23}H_{28}ClNO_5$ $[M+H]^+$ 434.1729, found 434.1735.

*4.12. 2-Acetamido-2-deoxy-5-chloro 5a-carba-α-D- glucopyranose (**9a**).*

To a stirred solution of compound **9** (0.018 g, 0.16 mmol) in methanol was added Palladium hydroxide (0.020 g, 20% weight on carbon, wet) at room temperature. The reaction mixture stirred under H_2 balloon pressure for 12 h. After completion of reaction, the reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness to furnish compound **9a** as a colourless sticky solid (0.009 g, 90%): $[\alpha]_D^{20}$ +36.0 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD); δ 4.02 (dd, *J* = 2.7 Hz and 5.7 Hz, 1H), 3.82 (dd, *J* = 2.7 Hz and *J* = 10.6 Hz, 1H), 3.75 (dd, *J* = 10.5 Hz and 1.6 Hz, 1H), 3.65 (d, *J* = 10.9 Hz, 1H, H-6a), 3.51 (d, *J* = 8.8 Hz, 1H, H-4), 3.47 (d, *J* = 10.9 Hz, 1H, H-6b), 2.04 (m, 4H, H-5a and NH*Ac*), 1.90 (dd, *J* = 2.8 Hz, 15.2 Hz, 1H, H-5a'); ^{13}C NMR (100 MHz, CD_3OD) δ 173.6, 77.1, 75.7, 71.1, 70.1 (C-3, C-4, C-5, C-1), 57.5 (C-6), 49.3 (C-2), 36.1 (C-5a), 22.7 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_9H_{16}ClNO_5$ $[M+H]^+$ 254.0795, found 254.0820.

4.13. General Procedure for the preparation of α-pseudo C-1 alkyl epoxides 10a-10c

To a stirred solution of sodium hydride (0.027 g, 1.13 mmol) in anhydrous DMF (2 mL) at 0 °C was added a solution of compound **8** (0.18 g, 0.45 mmol) in anhydrous DMF dropwise, after the addition the reaction mixture was stirred at same temperature for 10 min. Methyl iodide (0.07 mL, 1.13 mmol) was added dropwise to this reaction mixture and the reaction mixture was stirred at room temperature for 3 h. After completion (TLC) of reaction, the reaction mixture was quenched by addition of saturated NH_4Cl aqueous solution (25 mL) and extracted with ethyl acetate (3 × 20 mL), and combined organic layer was washed with brine solution, dried over

anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (Ethyl acetate/ hexane, 7:3) to furnished compound **10a** as a colorless solid (0.16 g) in 88% isolated yield. Similar reaction protocol was adopted for the preparation of compounds **10b** and **10c**.

4.13.1. Compound (***10a***). $[\alpha]_D^{20}$ – 17.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H, ArH), 6.46 (d, *J* = 8.4 Hz, 1H, NH), 4.82 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.76-4.73 (m, 1H, H-2), 4.66 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.54 (d, *J* = 11.6 Hz, 2H, CH_2Ph), 3.81 (t, *J* = 3.9 Hz, 1H, H-3), 3.69 (dt, *J* = 3.9 Hz and *J* = 10.8 Hz, 1H, H-1), 3.35 (s, 4H, OCH_3 and H-4), 2.67 (dd, *J* = 5.2, and 6.4 Hz, 2H, H-6), 2.25 (t, *J* = 12.0 Hz, 1H, H-5a), 1.81 (s, 3H, NH*Ac*), 1.48 (dd, *J* = 4.0 and 12.8 Hz, 1H, H-5a'); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.9 (NHCO), 137.86, 137.8 (ArqC), 128.7, 128.6, 128.1, 128.0, 127.8, 127.6 (ArC), 80.3, 78.1, 77.3, 75.8 (C-5), 73.1, 72.8, 75.3, 57.2, 57.0 (O*C*H_3 and, C-6), 50.6, 30.8 (C-5a), 23.6 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{24}H_{29}NO_5$ $[M+H]^+$ 411.2046, found 411.2051.

4.13.2. Compound (***10b***)

Compound **10b** was prepared starting from **8** (150 mg, 0.39 mmol) using DMF (5mL) and butyl bromide (0.07 mL, 1.17 mmol, 3.0 equiv) at elevated temperature (50 °C, 3 h) and pure product was isolated (Ethyl acetate/hexane 1:1) in 65% yield (112 mg). $[\alpha]_D^{20}$ – 14.3 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H, ArH), 6.39 (d, *J* = 8.0 Hz, 1H, N*H*), 4.81 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.71 (m, 1H, H-2), 4.67 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.54 (d, *J* = 11.6 Hz, 2H, CH_2Ph), 3.82 (t, *J* = 4.0 Hz, 1H, H-3), 3.74 (dt, *J* = 3.9 Hz and 10.8 Hz, 1H, H-1), 3.58 (dd, *J* = 6.4 Hz and 14.8 Hz, 1H, H-4), 3.35-3.30 (m, 2H, O-butyl), 2.69 (q, *J* = 4.0 Hz, 2H, H-6), 2.26 (t, *J* = 12.0 Hz, 1H, H-5a), 1.80 (s, 3H, NH*Ac*), 1.49-1.44 (m, 3H, CH_2 of butyl and H-5a'), 1.34-1.25 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H, CH_3 of butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (NHCO), 137.9, 137.8 (ArqC), 128.6, 128.0, 127.8, 127.7 (ArC), 80.3 (C-4), 78.1 (C-3), 77.3 (C-5), 74.1 (C-1), 73.0 (CH_2Ph), 72.9 (CH_2Ph), 69.0 (C-6), 57.3 (C-2), 32.0 (C-5a), 31.3, 23.6 (NH*Ac*), 19.4, 14.0 (CH_3 of butyl); HRMS (ESI) *m/z*: calcd for $C_{27}H_{35}NO_5$ $[M+H]^+$ 454.2588, found 454.2623.

4.13.3. Compound (***10c***)

Compound **10c** was prepared starting from **8** (80 mg, 0.20 mmol) using DMF (5mL) and hexyl bromide (0.06 mL, 0.40 mmol, 3.0 equiv) at elevated temperature (50 °C, 3 h) and pure product was isolated after flash chromatography (Ethyl acetate/hexane 7:3) in 64% yield (62 mg). $[\alpha]_D^{20}$ – 11.7 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.36-7.28 (m, 10H, ArH), 6.39 (d, *J* = 8.0 Hz, 1H, NH), 4.81 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.72-4.70 (m, H-2), 4.66 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.55 (t, *J* = 11.6 Hz, 2H, CH_2Ph), 3.82 (t, *J* = 4.0 Hz, 1H, H-3), 3.74 (dt, *J* = 3.9, 10.8 Hz, 1H, H-1), 3.57 (dd, *J* = 6.4, 14.8 Hz, 1H, H-4), 3.35-3.29 (m, 2H, hexyl), 2.66 (q, *J* = 4.0 Hz, 2H, H-6), 2.26 (t, *J* = 12.0 Hz, 1H, H-5a), 1.80 (s, 3H, NH*Ac*), 1.49-1.45 (m, 4H), 1.25 (m, 8H), 0.87 (t, *J* = 7.6 Hz, 3H, CH_3 of hexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (NH*C*O), 137.9, 137.8 (ArqC), 128.6, 128.1, 128.0, 127.8, 127.7 (ArC), 80.3 (C-4), 78.1 (C-3), 77.3 (C-5), 74.1 (C-1), 73.0 (*C*H_2Ph),72.8 (*C*H_2Ph), 69.3 (C-6), 57.3 (C-2), 31.8 (C-5a), 31.3, 29.9, 29.8, 25.8, 23.6 (NH*Ac*), 22.7, 14.1; HRMS (ESI) *m/z*: calcd for $C_{29}H_{39}NO_5$ $[M+H]^+$ 482.2901, found $[M+H]^+$ 482.2941.

4.14. General Procedure for the preparation of α-pseudo C-1 alkyl carbasugars 11a-11c.

4.14.1. Methyl 2-Acetamido-2-deoxy-3,4-di-O-benzyl-5-chloro 5a-carba-α-D- glucopyranoside (***11a***).

To a stirred solution of compound **10a** (0.08 g, 0.38 mmol) in anhydrous CH_2Cl_2 was added $TiCl_4$ (0.32 ml, 1M in CH_2Cl_2, 2.01 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. After completion (TLC) of reaction, the reaction mixture was quenched with sodium chloride solution (5 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash chromatography (Ethyl acetate / hexane 7:3) and compound **11a** was obtained as sticky oil (0.06 g) in 69% isolated yield: $[\alpha]_D^{20}$ + 28.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H, ArH), 5.54 (d, *J* = 8.8 Hz, 1H, NH), 4.94 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.86 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 4.72 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.64 (d , *J* = 11.2 Hz, 1H, CH_2Ph), 4.13 (td, *J* = 3.2 Hz and *J* = 10 Hz, 1H, H-2), 3.86 (t, *J* = 9.6 Hz, 1H, H-3), 3.75 (d, *J* = 9.6 Hz, 1H, H-4), 3.67 (m, 1H, H-1), 3.60 (d, *J* = 11.2 Hz, 1H, H-6a), 3.37 (s, 3H, OCH_3), 3.37-3.35 (m, 1H, H-6b), 2.08 (dd, *J* = 3.2 Hz, 15.0 Hz, 1H, H-5a),

1.83 (s, 3H, NH*Ac*), 1.81-1.80 (m, 1H, H-5a'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (NHCO), 138.4, 138.0 (ArqC), 128.7, 128.6, 128.38, 128.3, 128.2, 128.0 (ArC), 81.5, 79.0, 78.6 (C-3, C-4, C-1), 76.2 (C-5), 75.7, 75.3 (*C*H_2Ph), 58.2 (O*C*H_3), 53.6 (C-2), 48.0 (C-6), 31.4 (C-5a), 23.5 (NH*Ac*);. HRMS (ESI) *m/z*: calcd for $C_{24}H_{30}ClNO_5$ $[M+Na]^+$ 448.1885, found 448.1896.

*4.14.2. Butyl 2-Acetamido-2-deoxy-3,4-di-O-benzyl-5-chloro 5a-carba-α-D-glucopyranoside (**11b**).*

Compound **11b** was prepared starting from **10b** (0.1 g, 0.22 mmol) and pure product was isolated (Ethyl acetate/hexane 7:3) in 70% yield (76 mg) after purification. $[\alpha]_D^{20}$ + 23.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10H, ArH), 5.27 (d, *J* = 10.8 Hz, 1H, NH), 4.96 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.87 (d, *J* = 8 Hz, 1H, CH_2Ph), 4.74 (d, *J* = 12 Hz, 1H, CH_2Ph), 4.65 (d, *J* = 12 Hz ,1H, CH_2Ph), 4.21 (s, 1H, OH), 4.02 (td, *J* = 2.8, 10.8 Hz, 1H, H-2), 3.88 (t, *J* = 9.6 Hz, 1H, H-3), 3.80 (dd, *J* = 3.2 and 6.0 Hz, 1H), 3.73 (d, *J* = 11.5 Hz, 1H, H-6a), 3.65-3.60 (m, 2H, OCH_2 of Butyl) 3.35 (d, *J* = 10.4 Hz, 1H, H-6b), 3.26 (dt, *J* = 6.4 Hz and 9.2 Hz, H-1), 2.00 (dd , *J* = 3.2 Hz and 15.2 Hz, 1H, H-5a), 1.83 (dd, *J* = 2.4 Hz and 15.2 Hz, 1H, H-5a'), 1.78 (s, 3H, NH*Ac*), 1.53-1.45 (m, 2H, CH_2 of butyl), 1.35-1.25 (m, 2H, CH_2 of butyl), 0.89 (t, *J* = 7.6 Hz, 3H, CH_3 of butyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (NHCO), 138.4, 138.1 (ArqC), 128.78, 128.7, 128.5, 128.4, 128.1, 127.9 (ArC), 81.8 (C-4), 78.0 (C-3), 77.6 (C-5), 77.4, 76.4 (C-1), 75.8 (CH_2Ph),75.2 (CH_2Ph), 70.8 (C-6), 54.0 (C-2), 47.8, 32.3 (C-5a), 31.8, 23.4 (NH*Ac*), 19.3 (CH_2 of Butyl), 13.8 (CH_3 of Butyl); HRMS (ESI) *m/z*: calcd for $C_{27}H_{36}ClNO_5$ $[M+Na]^+$ 512.2174, found 512.2217.

*4.14.3. Hexyl 2-acetamido-2-deoxy-3,4-di-O-benzyl-5-chloro 5a-carba-α-D- glucopyranoside (**11c**).*

Compound **11c** was prepared starting from **10c** (0.04 g, 0.08 mmol) and pure product was isolated (Ethyl acetate/hexane 7:3) in 72% yield (31 mg). $[\alpha]_D^{20}$ + 21.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.25 (m, 10H, ArH), 5.28 (d, *J* = 9.2 Hz, 1H, NH), 4.96 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 4.87 (d, *J* = 11.6 Hz, 1H, CH_2Ph), 4.74 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 4.66 (d , *J* = 12.0 Hz , 1H, CH_2Ph), 4.21 (s, 1H, OH), 4.03 (td, *J* = 3.2 Hz, *J* = 10.7 Hz, 1H, H-2), 3.88 (t, *J* = 9.2 Hz, 1H, H-3), 3.80 (dd, *J* = 3.2 Hz, 1H), 3.74 (d, *J* = 9.2 Hz, 1H), 3.65-3.61 (m, 2H, O*C*H_2 of hexyl), 3.35 (d, *J* = 12 Hz, 1H, H-6a) 3.26 (dt, *J* = 7.2 Hz, J = 15.1 Hz, 1H, H-1), 1.99 (dd , *J*

= 3.2, 15.2, 1H, H-5a), 1.86 (dd, *J* = 2.3, 15.0 Hz, 1H, H-5a'), 1.78 (s, 3H, NH*Ac*), 1.50-1.48 (m, 2H), 1.29-1.25 (m, 7H), 0.88 (t, *J* = 7.6 Hz, 3H, CH_3 of hexyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (NHCO), 138.4, 138.1 (ArqC), 128.78, 128.7, 128.6, 128.5, 128.4 128.1, 128.0 (ArC), 81.7, 78.2 (C-3, C-4), 76.4 (C-5), 75.8, 75.2 (CH_2Ph), 71.1, 54.0, 47.8 (C-2, C-6), 32.3, 31.6 (C-5a), 29.8, 25.8, 23.5 (NH*Ac*), 22.7, 14.1 (CH_3 of hexyl); HRMS (ESI) *m/z*: calcd for $C_{29}H_{40}ClNO_5$ $[M+H]^+$ 518.2668, found 518.2718.

4.15. General Procedure for the preparation of α-pseudo C-1 alkyl carbasugars 12a-12c.

*4.15.1. Methyl 2-acetamido-2-deoxy-5-chloro 5a-carba-α-D- glucopyranoside (**12a**).*

To a stirred solution of compound **11a** (0.05 g, 0.11 mmol) in methanol was added Palladium hydroxide (0.020 g, 20% weight on carbon, wet) in methanol (5 mL) at room temperature. The reaction mixture was stirred under H_2 gas balloon pressure for 12 h. The reaction mixture was filtered through celite, and the filtrate was evaporated to dryness to furnish compound **12a** as a colorless sticky solid (0.025 g, 83%): $[\alpha]_D^{20}$ + 37.0 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, D_2O) δ 3.92-3.82 (m, 2H), 3.74 (s, 1H), 3.66 (brs, 2H), 3.62 (d, *J* = 11.2 Hz, 1H, H-6b), 3.42 (s, 3H, OCH_3), 2.40 (dd, *J* = 3.6 Hz and 16.0 Hz, 1H, H-5a), 2.09 (s, 3H, NH*Ac*), 1.80 (d, *J* = 12.0 Hz, 1H, H-5a'); ^{13}C NMR (125 MHz, D_2O) δ 176.7 (NHCO), 80.7 (C-3), 77.8 (C-4), 76.5 (C-5), 72.0 (C-1), 60.5 (C-2), 57.3 (OCH_3), 51.5 (C-6), 33.3 (C-5a), 24.5 (NH*Ac*); HRMS (ESI) *m/z*: calcd for $C_{10}H_{18}ClNO_5$ $[M+Na]^+$ 290.0766, found 290.0770.

*4.15.2. Butyl 2-acetamido-2-deoxy-5-chloro 5a-carba-α-D- glucopyranoside (**12b**).*

Compound **12b** was prepared starting from **11b** (60 mg, 0.122 mmol) and pure product was obtained in 78% yield (35 mg). $[\alpha]_D^{20}$ +34.0 (*c* 0.2, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 3.85-3.84 (m, 1H), 3.79-3.77 (m, 2H), 3.67-3.61 (m, 2H), 3.48-3.41 (m, 3H), 2.18 (dd, *J* = 2.8, 15.6 Hz, 1H, H-5a), 2.15 (s, 3H, NH*Ac*), 1.69 (dd, *J* = 2.8 Hz and 15.6 Hz, 1H, H-5a'), 1.58-1.52 (m, 2H), 1.42-1.29 (m, 2H), 0.93 (q, *J* = 7.6 Hz, 3H, CH_3 of hexyl); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4 (NHCO), 78.5, 76.5, 75.8, 72.0, 71.0, 56.7, 32.9, 32.8, 22.5 (NH*Ac*), 20.1 14.1; HRMS (ESI) *m/z*: calcd for $C_{13}H_{24}ClNO_5$ $[M+H]^+$ 310.1415, found 310.1445.

*4.15.3. Hexyl 2-acetamido-2-deoxy-5-chloro 5a-carba-α-D- glucopyranoside (**12c**).*

Compound **12c** was prepared starting from **11c** (30 mg, 0.057 mmol) and pure product was obtained in 77% yield (15 mg). $[\alpha]_D^{20}$ + 30.5 (*c* 0.2, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 3.85 (dd, *J* = 2.0 Hz, 1H), 3.79-3.77 (m, 2H), 3.67-3.61 (m, 2H), 3.49-3.46 (m, 2H), 3.43 (dt, *J* = 6.4 Hz, J = 9.6 Hz, 1H), 2.16 (dd, *J* = 3.2 Hz and *J* = 15.6 Hz, 1H, H-5a), 2.00 (s, 3H, NH*Ac*), 1.80 (dd, *J* = 2.8 Hz, 15.6 Hz, 1H, H-5a'), 1.59-1.56 (m, 2H), 1.38-1.28 (m, 6H), 0.91 (t, *J* = 6.4 Hz, 3H, CH_3 of hexyl); ^{13}C NMR (100 MHz, CD_3OD) δ 78.5, 76.5, 75.8, 72.3, 71.0, 56.7, 33.0, 32.7, 30.7, 26.7, 23.6 (NH*Ac*), 22.6, 14.3; HRMS (ESI) *m/z*: calcd for $C_{15}H_{28}ClNO_5$ $[M+H]^+$ 338.1729, found 338.1756.

Appendix A. Supplementary data

Supplementary data related to this article can be found at DOI: XXXX.

These data includes ^{1} H, ^{13} C NMR spectra for all new compounds and for previously reported compounds. The data also includes ^1H-^1H COSY and ^1H-^{13}C HSQC spectra of selected new compounds. Reaction optimization for synthesis of **5a**, **6a,** IBX mediated oxidation of **6b** and transition states of stereoselecetive epoxidation on **5a**. (PDF)

Author Information

Corresponding Author

*E-mail: ram.sagar@snu.edu.in

Acknowledgements

Authors are thankful to the Shiv Nadar University (SNU) for providing required lab facilities. CN and PK are thankful to Council of Scientific and Industrial Research (CSIR), India for junior research fellowships. Authors are also thankful to the Department of Science and technology (DST) India for financial support (DST-EMR/2014/000320). This work was supported by Grant-in-Aid for Scientific Research (C) (No: JP17K08362) (AK) from the Japanese Society for the Promotion of Science (JSPS).

References

1. Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919–2036.
2. McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516–1521.
3. Witte, M.; Kallemeijn, W. W.; Aten, J.; Li, K.-Y.; Strijland, A.; Donker-Koopman, W. E.; Van Den Nieuwendijk, A. M. C. H.; Bleijlevens, B.; Kramer, G.; Florea, B. I.; Hooibrink, B.; Hollak, C. E. M.; Ottenhoff, R.; Boot, R. G.; Van Der Marel, G. A.; Overkleeft, H. S.; Aerts, J. M. F. G. *Nat. Chem. Biol.* **2010**, *6*, 907–913.
4. Ghavre, M.; Froese, J.; Pour, M.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 5642−5691.
5. Leclerc, E.; Pannecoucke, X.; Ethève-Quelquejeu, M.; Sollogoub, M. *Chem. Soc. Rev.* **2013**, *42*, 4270–4283.
6. Lünse, C. E.; Schmidt, M. S.; Wittmann, V.; Mayer, G. *ACS Chem. Biol.* **2011**, *6*, 675**–**678.
7. Dwek, R. A.; Butters, T. D.; Platt, F.; Zitzmann, N. *Nat. Rev. Drug Discov.* **2002**, *1*, 65−75.
8. Collins, P.J.; Haire, L. F.; Lin, Y. P.; Liu, J.; Russell, R. J.; Walker, P.A.; Skehel, J. J.; Martin, S. R.; Hay, A. J.; Gamblin, S. J. *Nature* **2008**, 453, 1258–1261.
9. Lahiri, R.; Ansari, A. A.; Vankar, Y. D. *Chem. Soc. Rev.* **2013**, *42*, 5102–5118.
10. Jayakanthan, K.; Vankar, Y. D. *Org. Lett.* **2005**, *7*, 5441–5444.
11. Ansari, A. A.; Rajasekaran, P.; Khan, M. M.; Vankar, Y. D. *J. Org. Chem.* **2014**, *79*, 1690−1699.
12. Harit, V. K.; Ramesh, N. G. *J. Org. Chem.* **2016**, *81*, 11574–11586.
13. Mondal, S.; Sureshan, K. M. *J. Org. Chem.* **2016**, *81*, 11635–11645.
14. Gómez, A. M.; Uriel, C.; Company, M. D.; and López, J. C. *Eur. J. Org. Chem.* **2011**, 7116–7132.
15. Gómez, A. M.; Moreno, E.; Valverde, S.; and López, J. C. *Eur. J. Org. Chem.* **2004**, 1830–1840.
16. Lalk, M.; Reinke, H.; and Peseke, K. *Eur. J. Org. Chem.* **2001**, 759–765.
17. Shan, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3381–3384.
18. Shan, M.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 2986–2989.
19. Ng, W-L.; Li, H-C.; Lau, K-M.; Chan, A. K. N.; Lau, C. B-K.; Shing, T. K. M. *Sci. Rep.* **2017**, *7*, 5581 and references cited therein.

20. (a) Barton, D. H. R.; Géro, S. D.; Augy-Dorey, S.; Quiclet-Sire, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1399–1401. (b) Barton, D. H. R.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumény, J. M.; Géro, S. D.; Quiclet-Sire, B.; Stütz, P. *Tetrahedron* **1990**, *46*, 215−230.
21. (a) Ogawa, S.; Iwasawa, Y.; Nose, T.; Suami, T.; Ohba, S.; Ito, M.; Saito, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 903−906. (b) Ogawa, S.; Aoyama, H.; Sato, T. *Carbohydr. Res.* 2002, *337*, 1979−1992. (c) Ogawa, S.; Funayama, S.; Okazaki, K.; Ishizuka, F.; Sakata, Y.; Doi, F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5183−5188.
22. Sun, Y.; Nitz, M. *J. Org. Chem.* **2012**, *77*, 7401−7410.
23. Goyal, N.; Mangunuru, H. P. R.; Parikh, B.; Shrestha S. and Wang, G. *Beilstein J. Org. Chem.* **2014**, *10*, 3111–3121.
24. Roy, A.; Ray, A. K.; Mukherjee, A.; Roy, N. *Indian J. of Chem., Sec B*: **1987**, *26B*, 1165-1167.
25. Falcone-Hindley, M.L. and Davis, J. T. *J. Org. Chem.* **1998**, *63*, 5555–5561.
26. Scaffidi, A.; Stubbs, K. A.; Vocadlo, D. J.; Stick, R. V. *Carbohydr Res.* **2008**, *343*, 2744–2753.
27. Petasis, N. A.; Bzowej, E. I.. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394.
28. Takai, K.; Tadahiro, K.;Yasutaka, K. *J. Org. Chem.*, **1994**, *59*, 2668–2670.
29. Hamlin, T. A.; Kelly, C. B.; Cywar, R. M.; Leadbeater, N. E. *J. Org. Chem.* **2014**, *79*, 1145–1155.
30. Sollogoub, M.; Pearce, A. J.; Hérault, A. and Sinaÿ, P. *Tetrahedron: Asymmetry* **2000**, *11*, 283–294.
31. (a). Williams, S. J.; Withers, S. G. *Carbohydr Res.* **2000**, *327*, 27–46. (b) Skelton, B. W.; Stick, R. V.; Stubbs, K. A.; Watts, A. G; White, A. H. *Aust. J. Chem.* **2004**, *57*, 345-353.
32. Kuno, S.; Higaki, K.; Takahashi, A.; Eiji Nanbab, E. and Ogawa, S. *Med. Chem. Commun.* **2015**, *6*, 306–310.
33. Bouquet, J.; King, D. T.; Vadlamani, G.; Benzie, G. R.; Iorga, B.; Ide, D.; Adachi, I.; Kato, A.; Vocadlo, D. J.; Mark, B. L.; Blériot, Y. and Désiré, J. *Org Biomol Chem.* **2017**, 15, 4609–4619.