A Platinum Open Access Journal for Organic Chemistry

Paper

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Arkivoc **2022**, part vi, 0-0

to be inserted by editorial office

Synthesis of (5,6 & 6,6)-oxa-oxa annulated sugars as glycosidase inhibitors from 2-formyl galactal using iodocyclization as a key step

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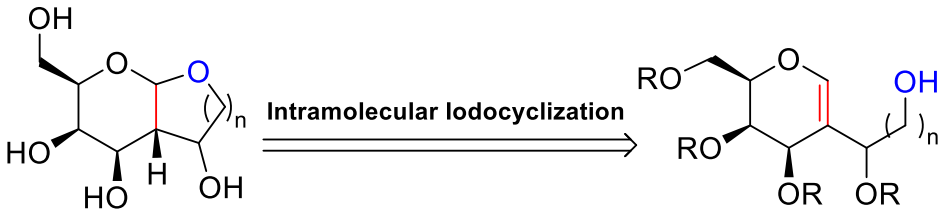
This paper is dedicated to Professor Sambasivarao Kotha on the occasion of his 65th birthday

Received 06-19-2022 **Accepted Manuscript** 08-02-2022 **Published on line** 08-14-2022

Abstract

Oxa-oxa (5,6 & 6,6) annulated sugars were synthesized from 2-formyl galactal using iodocyclization as a key step. The glycosidase inhibitory activities of the synthesized molecules were tested against commercially available enzymes which showed that the sugar-furan molecules are potent and selective inhibitors.



Annulated Sugars

Keywords: Iodocyclization, 2-formyl galactal, annulated sugars, glycosidase inhibitors

Introduction

Structurally modified carbohydrates act as potential mimetics of naturally occurring sugars and represent targets for the development of antiviral, antibacterial and other biological/medicinal activities.[1-6] *C*-branched sugars,[5-9] annulated sugars,[5-6,10-11] and *C*-glycosides[5-6,12-17] are some of the most important classes of structurally modified carbohydrates. Among these modified sugars, annulated sugars have received increasing attention in organic synthesis.[10,11] This is mainly because the fused-bicyclic moiety (or annulated sugars) containing a pyranose ring is a common structural feature in various biologically important natural products.[18-24] For example, halichondrins[18] **1** (Figure 1) are a group of polyether macrolides which contain many substituted tetrahydropyrans annulated with each other and also with tetrahydrofuran rings, and are known to possess anticancer activity. Likewise, bradyrhizose[19] **2** possesses significant biological activity relevant to a new mechanism of nitrogen fixation. Peltalosa[21] **3**, isolated from the roots of the Mexican plant *Psacalium peltatum*, is associated with hypoglycemic activity and is likely to be useful in treating diabetes. Dysiherbaine **4** and Neodysiherbaine **5** (Figure 1) possess[23,24] unique agonist activity with the non-NMDA type glutamate receptors and kainate receptors.

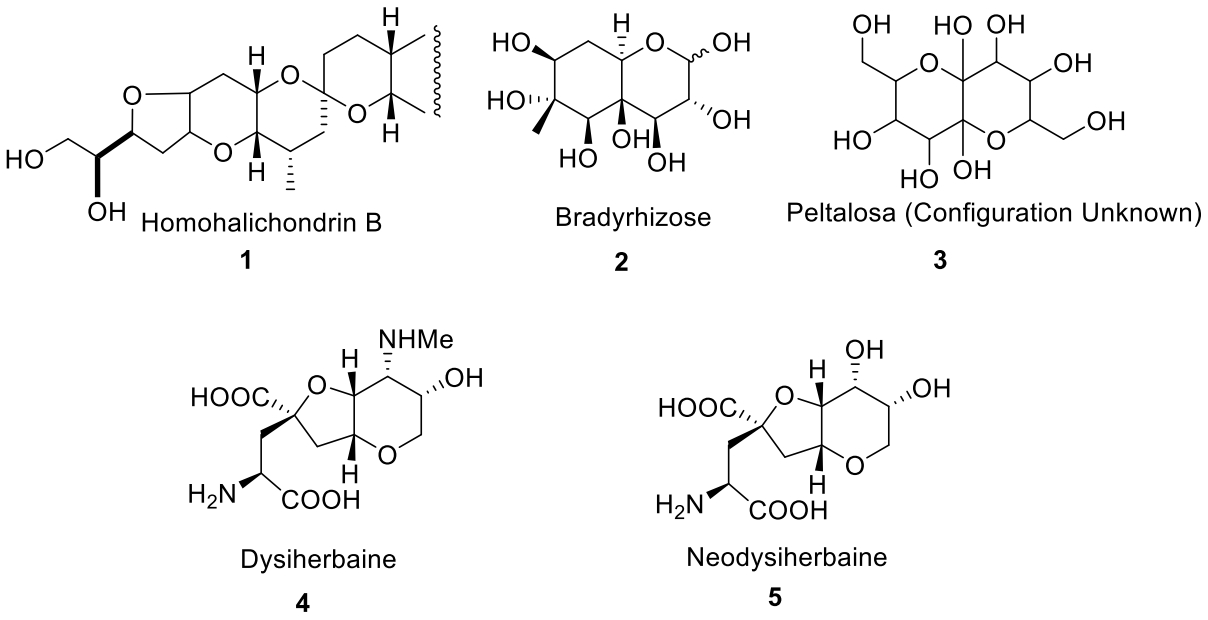


Figure 1. Fused bicyclic moiety contains molecules.

Thus, synthesis of annulated sugars has been of interest to synthetic chemists and is an important area of research in modern drug discovery. Many groups have been involved in the synthesis of annulated sugars[10,11] in the recent past. A few examples[25-28] include synthesis of sugar-fused furan derivative **6**, 1,2-annulated 1,3-oxazine **7**, sugar-fused chroman **8** and furofuryl glycal **9** as shown in Figure 2. In addition to this, our group also has been actively involved in synthesis of several 1,2-annulated sugar molecules[29-36] which exhibit interesting glycosidase inhibitory behavior. These include sugar-pyrrolidine hybrid **10**,[29] sugar morpholinone fused molecule **11**[30] and sugar-piperidine hybrids **12**[31] and **13**[32] as shown in Figure 2. In 2016 Ziegler and co-workers synthesized[37] similar kind of 1,2-annulated sugars namely polyhydroxylated[5-6,28] dioxadecalins **14** using ring closing metathesis as a key reaction.

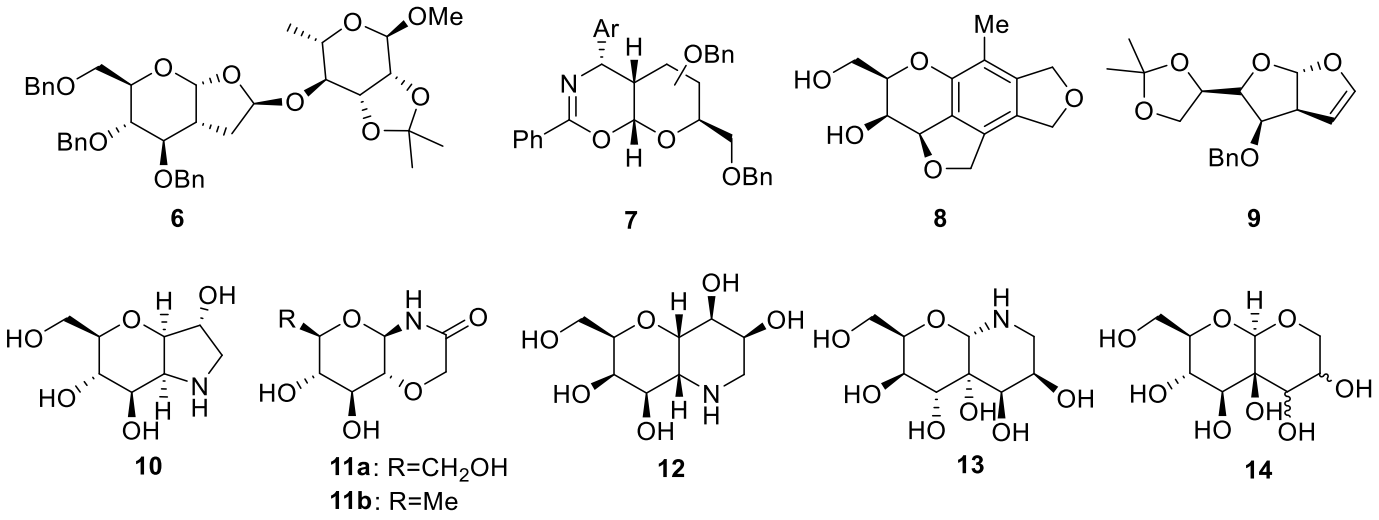


Figure 2. Annulated sugars reported in literature.

In view of these reports and our continued interest in the design and synthesis of annulated sugars, we planned to develop an efficient approach for the synthesis of structurally modified new 1,2-annulated sugars as potential glycosidase inhibitors. Thus, herein we report synthesis of (5,6 & 6,6)-oxa-oxa annulated sugars starting from 2-formyl galactal and by using iodocyclization as a key step, and report their glycosidase inhibition activities.

Results and Discussion

We were interested in the synthesis of a new type of structurally modified annulated sugars namely 1,2-annulated sugar-pyran and sugar-furan fused molecules. This was planned based on our earlier findings related to the synthesis of a new class of annulated sugars, including compound **13** (Figure 2), in which the ring oxygen of the parent sugar ring was one carbon (anomeric carbon) away from another ring hetero-atom (compounds **i-iii** Figure 3) of O-C-X type.

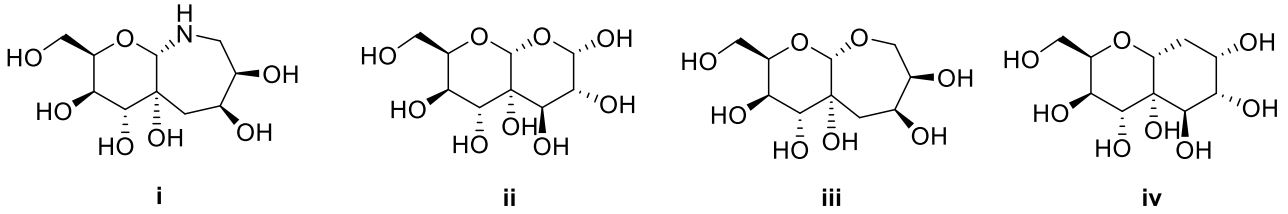


Figure 3. Structures of synthetic 1,2-annulated sugars with glycosidase inhibitory activities.

It was observed that, among these molecules, compound **13** was the best with respect to selectivity and extent of inhibition (IC_{50} = ~38.8 μM) and compound **iv** was the worst which is devoid of a hetero-atom X in the second ring. This supported our hypothesis that the presence of the hetero-atom X could lead to the species **B** and **C** (Figure 4) wherein the oxocarbenium ion part could easily mimic the accepted transition state

and the anionic part may involve in hydrogen bonding with the amino acids near the enzyme active site, and thereby provide a driving force for better and perhaps selective inhibition.

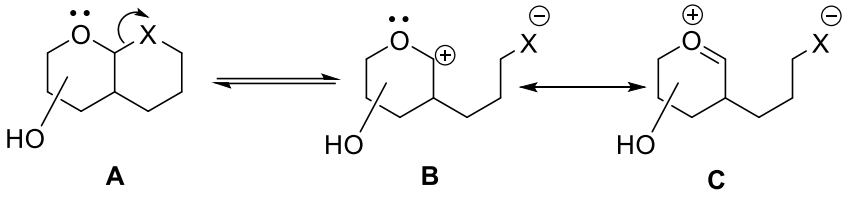


Figure 4. Schematic concept for the development of glycosidase inhibitors.

The newly designed molecules **I-III** are shown in Figure 5 in which one of them bears a hydrophobic butyl group. This was planned with a view to minimize the number of hydroxyl groups and increase some amount of hydrophobicity to assess their effects on the selectivity and the extent of inhibitions. The target molecules were envisioned to be obtained *via* iodocyclization of the corresponding primary alcohols **IV** and **V**, followed by dehalogenation. These primary alcohols could be obtained from olefins **VI** and **VII** whose side chains can be accessed by addition of vinyl and allyl magnesium bromides on 2-formyl galactal **15**.

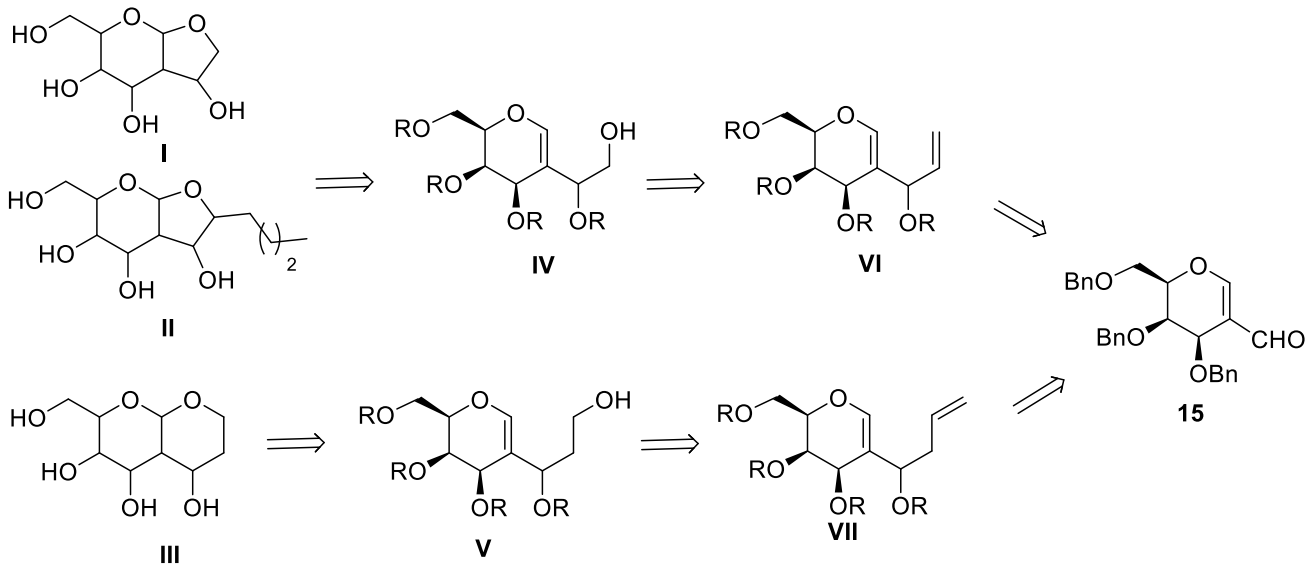
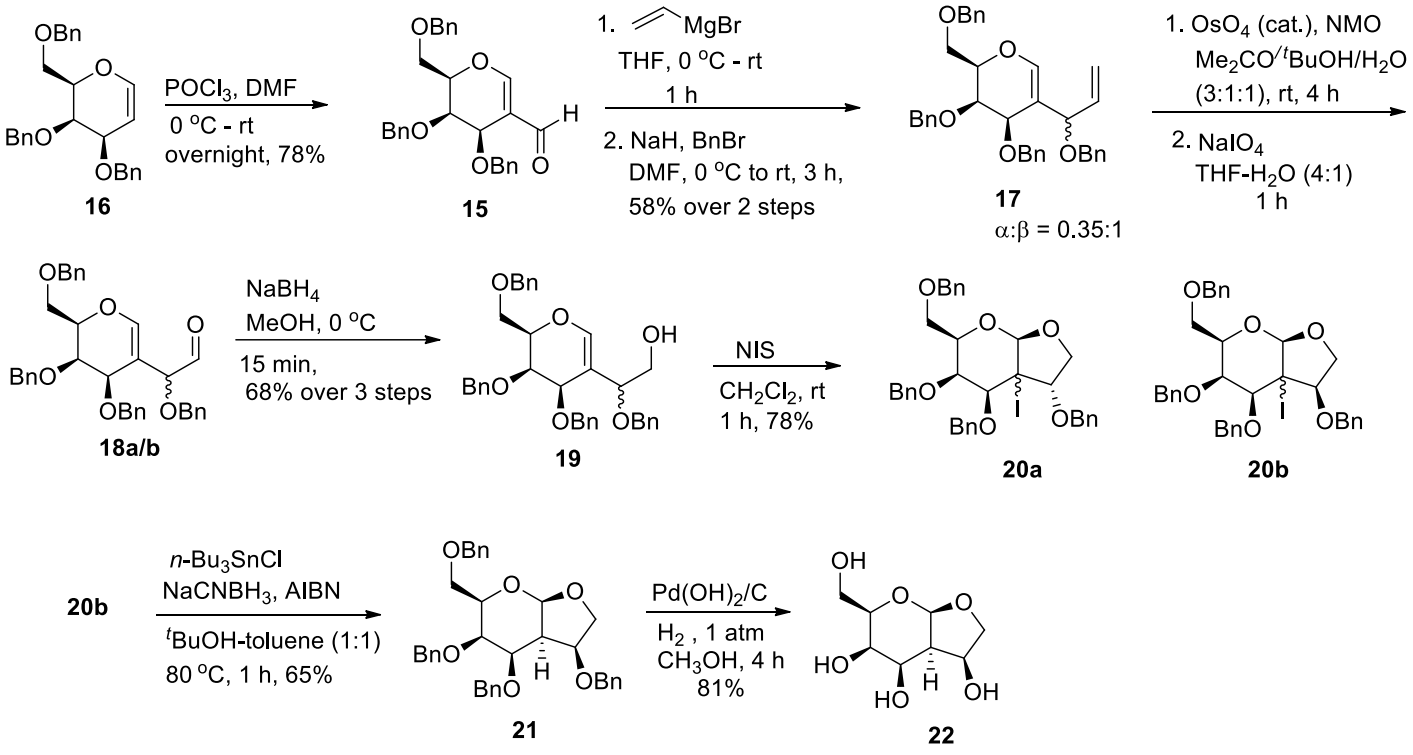


Figure 5. Schematic retrosynthesis of 1, 2-annulated sugars **I-III.**

C2-formyl glycals are versatile synthons in organic chemistry[38] as has been illustrated in the synthesis of many biologically important natural products, and synthetic analogues and intermediates. From our group also, we have exploited the potential of *C*-2-formyl group in the synthesis of sugar β-amino acids,[39] iminosugars,[40] hybrid molecules[36] and *C*-2-methylene glycosides.[41]

In the present study, synthesis of the designed 1,2-annulated sugars **I-III** commenced from 3,4,6-tri-*O*-benzyl-D-galactal **16** (Scheme 1) which was converted to the vinyl aldehyde **15** using the Vilsmeier-Haack reaction.[42] To this vinyl aldehyde was added vinylmagnesium bromide at 0 °C in dry THF. The resultant hydroxyl group was protected using benzyl bromide and sodium hydride forming the benzyl ether **17** in 58% yield over two steps (Scheme 1). The regioselective dihydroxylation of terminal alkene in **17** was carried out

using OsO_4/NMO to form a mixture of diols which was subsequently exposed to oxidative cleavage using sodium metaperiodate in THF/H_2O (1:1) medium at room temperature to afford the corresponding aldehyde **18a/b**. The aldehyde was then reduced with $NaBH_4$ in methanol affording the diastereomeric mixture of alcohols **19** (Scheme 1) which was chromatographically difficult to separate. Thus, this mixture of primary alcohols **19** was subjected to iodocyclization (Scheme 1) using *N*-Iodosuccinimide (NIS)[43]at room temperature in CH_2Cl_2 to form 6-*endo* iodocyclized products **20a** and **20b**. The acetals **20a** (20%) and **20b** (58%) were obtained in a 0.35:1 ratio in 78% yield which were easily separable by column chromatography at this stage. The major isomer **20b** was then subjected to radical mediated deiodination using a catalytic amount of *n*-Bu_3SnCl and AIBN in presence of $NaBH_3CN$ in toluene and ^{t}BuOH (1:1) at 80 °C for 1 h resulting in the formation of the desired product **21** in 65% yield. Deprotection of the benzyl groups in **21** with $Pd(OH)_2$/C in MeOH under 1 atm H_2 for 4 h afforded furan-fused sugar molecule **22** in 81% yield.



Scheme 1. Synthesis of sugar-furan fused molecule **22.**

The structure and stereochemistry of compound **22** was determined by ^{1}H NMR, COSY, nOe (Figure 6) and DEPT experiments.[44] The DEPT-135 analysis of compound **22** clearly showed two negative peaks corresponding to the carbons *C*-6 and *C*-7. In the nOe experiment, H-1 signal at *δ* 5.14 showed positive correlations with H-3 and H-8 protons at *δ* 4.41−4.39 and *δ* 4.38−4.34 respectively. Also, the H-5 signal at *δ* 3.72−3.67 (including H-6' and H-7') showed positive correlation with H-1 and H-3 signals. This suggests that H-5, H-1, H-3 and H-8 are in cis-orientation with respect to each other. In addition, irradiation of H-2 signal at *δ* 2.66 showed enhancement of H-4 signal at *δ* 4.07−4.05. This concludes that H-2 and H-4 are *cis* to each other. Further, the coupling constant of *J* = 4.0 Hz observed for H-1 which appeared as a doublet due to its coupling with H-2 indicates *cis*-relationship between them. Accordingly, the structure of compound **22** was confirmed to be as shown in Figure 6.

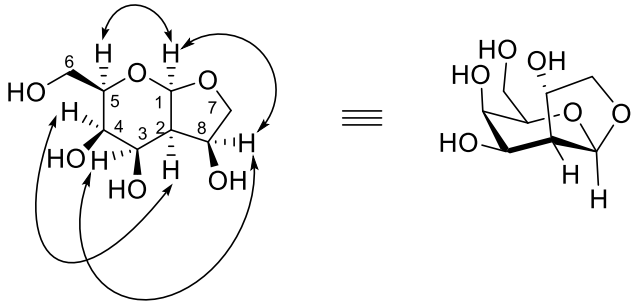
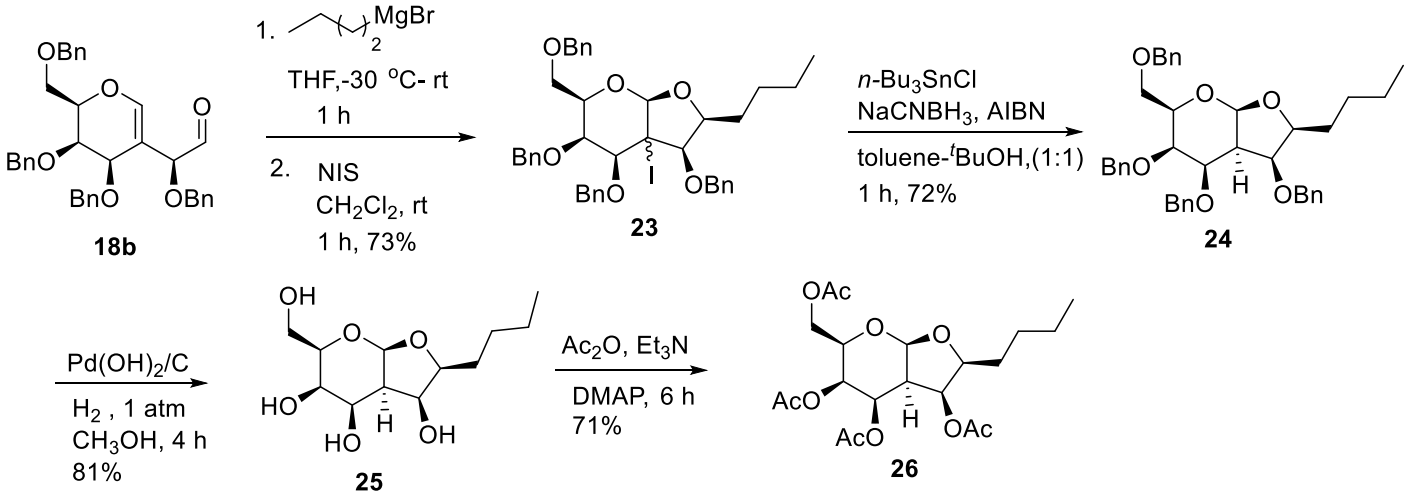


Figure 6. NOE correlations of compound **22.**

For the synthesis of n-butyl substituted sugar-furan hybrid molecule, a careful column chromatographic separation of aldehyde **18b** (β isomer) from the diastereomeric mixture of **18a**/**b** was done to perform the Grignard reaction. A freshly prepared *n*-butylmagnesium bromide was reacted with aldehyde **18b** at -30 °C (Scheme 2) to provide the corresponding alcohol. The crude alcohol was then subjected to iodocyclization to give a furan-fused sugar derivative **23** as a single compound. Compound **23** upon radical deiodination to obtain **24** followed by hydrogenation, as described earlier, afforded the desired annulated sugar derivative **25**. The free hydroxyl groups of compound **25** were protected as acetates using a 1:1 mixture of acetic anhydride and Et_3N in presence of DMAP over 6 h (Scheme 2) to afford peracetylated compound **26**.



Scheme 2. Synthesis of compound **26.**

The absolute configuration of the newly generated stereocenters was determined with the help of ^{1}H NMR, COSY, and nOe experiments.[44] Thus, in the nOe experiment of compound **26**, the H-5 signal at δ 3.79 showed positive correlations (Figure 7) with H-1 and H-3 signals at δ 5.33−5.15 (including H-1, H-3 and H-4) which indicated that H-5 and H-1 are *cis* to each other. The H-1 signal at δ 5.33−5.15 showed positive correlations with H-7 signal at δ 4.52 and H-8 signal at δ 6.02 ppm suggesting that H-1 is in *cis*-orientation both with H-7 and H-8. Also, irradiation of H-2 at δ 2.74 showed enhancement of signals for H-4 at δ 5.33−5.15 and H-7 at δ 4.52 suggesting that H-2 is *cis* to both H-4 and H-7. In the ^{1}H NMR spectrum of compound **26**, the signal for H-1 was observed to merge with the signals for H-3 and H-4. On the other hand, the signal for H-1 in compound **24** (benzyl protected compound) appeared as a clean doublet with a coupling constant of J = 4.4 Hz. Based on these data, the structure of **26** was deduced to be as shown in Figure 7.

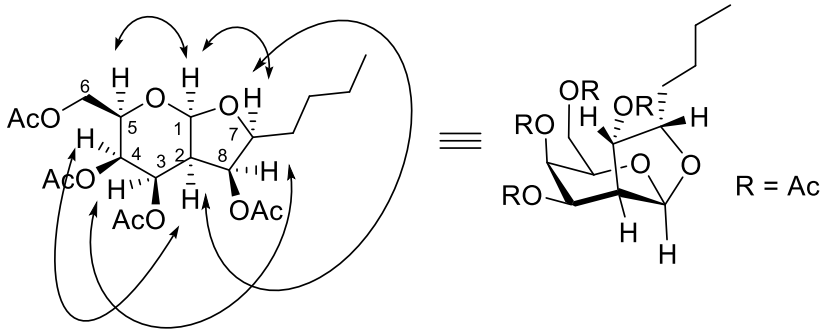
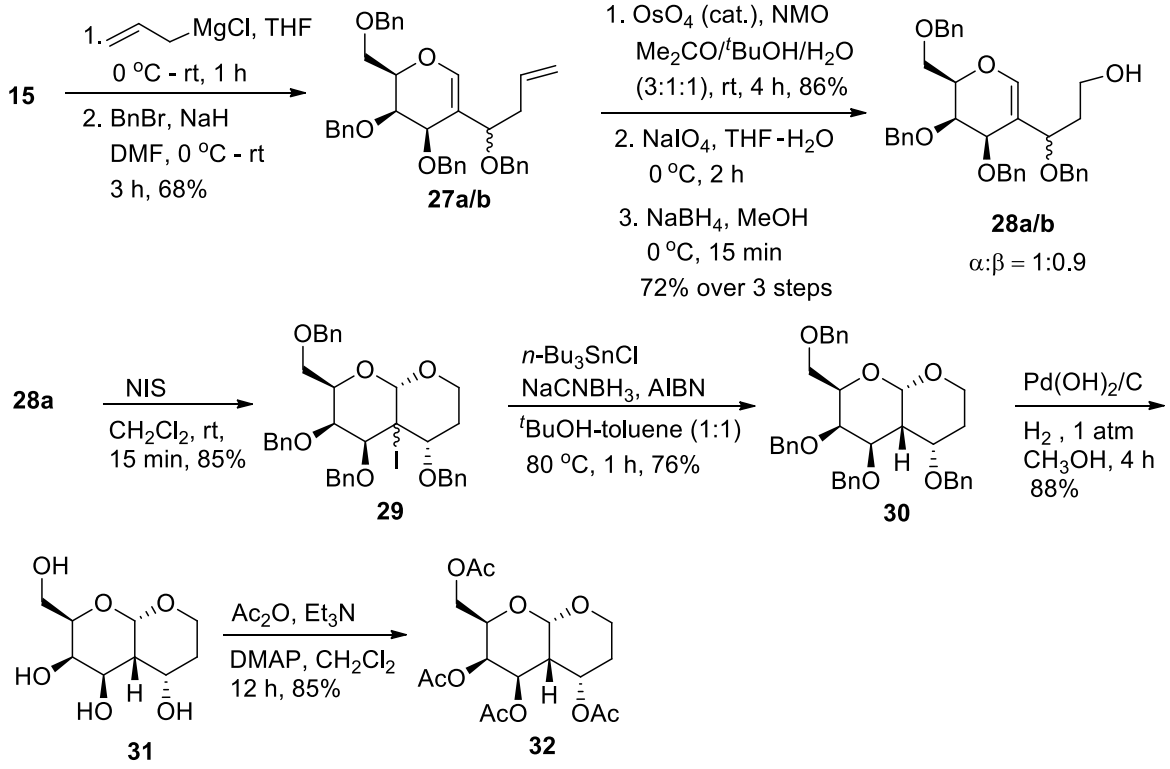


Figure 7. NOE correlations of compound **26.**

In a similar manner, sugar-pyran annulated molecule **32** was obtained by reacting 2-formyl galactal **15** with allylmagnesium bromide, followed by hydroxyl group protections as benzyl ethers to form **27** as a 1:0.9 (α and β). This mixture of **27** was subjected to the same sequence of reactions as described earlier *viz*. dihydroxylation, oxidative cleavage, $NaBH_4$ reduction *etc*., to provide a diastereomeric mixture **28a**/**b** (Scheme 3) of the primary alcohols. From this mixture of **28a**/**b** was separated the isomer **28a** in pure form which was subjected to a similar set of reactions such as iodocyclization, radical deiodination and hydrogenation reactions to afford sugar-pyran fused molecule **31** (Scheme 3).



Scheme 3. Synthesis of sugar-pyran fused molecule **32.**

The structure and stereochemistry of compound **31** was determined from the spectral data of the corresponding acetate **32** by using ^{1}H NMR, COSY, and nOe experiments.[44] Thus, in nOe experiments, irradiation of proton H-3 at δ 5.53, no enhancement was observed for H-7 at δ 5.07 indicating that H-3 and H-7 are in *trans* oriented with respect to each other. Further, irradiation of H-1 at δ 4.82 led to the enhancement

of the signal for proton H-7 at *δ* 5.07 and no enhancement was observed for H-3 and H-5 protons suggesting that H-1 and H-7 are in *cis* orientation. On the other hand, when H-2 at *δ* 2.54 was irradiated no correlation was observed with H-4 indicating that H-2 and H-4 are in *trans* orientation. In addition, the coupling between H-1 with H-2 led to a doublet at *δ* 4.83 with J = 3.50 Hz. Based on these spectral data, the structure of compound **32** is assigned to be as shown in Figure 8.

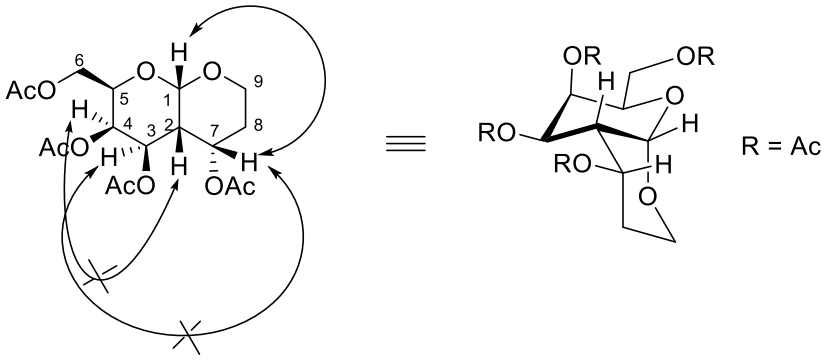
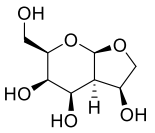
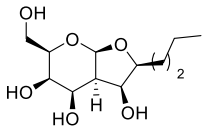
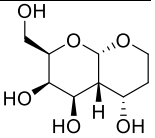


Figure 8. NOE correlations of compound **32.**

Table 1. Inhibition Values (IC_{50} in μM) of Synthesized Compounds

Compounds	 **22**	 **25**	 **31**
α-glucosidase (baker's yeast)	NI	NI	12.1
β–glucosidase (almonds)	NI	NI	NI
α-galactosidase (coffee beans)	NI	NI	NI
β–galactosidase (bovine liver)	NI	8.1	26.2
α-mannosidase (Jack beans)	8.8	NI	16.0
β–mannosidase (*Helix pomatia*)	NI	NI	NI
α-glucosidase (*rice*)	NI	NI	NI
α-L-fucosidase (*Bovine liver*)	NI	NI	NI

The hence obtained annulated molecules were then examined for their glycosidase inhibitory behaviour.[32,45] They were tested against 8 commercially available enzymes and the results are summarized in Table 1 wherein the IC_{50} values are indicated in μM. The *n*-butyl substituted sugar-furan molecule **25** was

found to be quite potent and highly selective against β–galactosidase (bovine liver source) with IC_{50} value being 8.1 μM. In addition, sugar-furan fused molecule **22** showed good and selective inhibition against α-mannosidase (Jack beans), with IC_{50} value to be 8.8 μM. On the other hand, sugar-pyran fused molecule **31** showed non-specific moderate inhibition against α-glucosidase, β-galactosidase and α–mannosidase, with IC_{50} values of 12.1 μM 26.2 μM and 16.0 μM respectively. From these studies it is clear that furan-fused sugar molecules (smaller in ring size) showed stronger inhibitory properties and presence of hydrophobic butyl group (cf. **25**) appeared to influence the activity in a positive way, making it to be equally good inhibitor as the corresponding parent molecule namely **22**. On comparing these results with our earlier work[32] (cf. compounds **13** and **i-iii**), it is obvious that our hypothesis as shown in Figure 4 is valid for the present set of compounds. Interestingly, even O-C-O type of molecules having pyran-furan fused rings are better than pyran-piperidine fused compound namely **13**, suggesting that decreasing the size of the ring and thereby decreasing the number of carbon atoms, and also decreasing the number of –OH groups influence the selectivity as well as the IC_{50} value irrespective of whether or not 'X' in O-C-X type arrangement is 'N'. Although it is not very clear how does the hydrophobic side chain affect the selectivity, but it is obvious that species of type **B** and **C** (Figure 4) that should form with both **22** and **25**, as well as with **31** do influence the inhibition data. It would be of interest to synthesize molecules of similar type but with an arrangement of O-C-N type and study their inhibition behavior. Work towards this direction will be a subject of future studies.

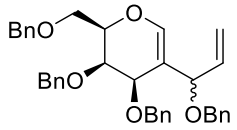
Conclusions

We have synthesized 1,2-linearly fused (5,6& 6,6)-oxa-oxa annulated sugars. The synthesis of these annulated molecules was achieved from 2-formyl galactal in short sequences and good yields via Grignard addition and halocyclization as key steps. Glycosidase inhibition studies revealed that the sugar-furan and *n*-butyl substituted sugar-furan molecules were most active and highly selective inhibitors.

Experimental Section

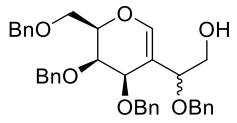
General. All experiments were performed in oven-dried apparatus and under nitrogen atmosphere in dry solvents, unless indicated otherwise. Commercial grade solvents were dried by known methods, and dry solvents were stored over 4 Å molecular sieves. IR spectra were recorded as a thin film and expressed in cm^{-1}. Mass spectra were obtained using Q-TOF apparatus from high resolution ESI mass spectrometer. ^1H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts have been reported in ppm downfield to tetramethylsilane and coupling constants expressed in Hertz (Hz); splitting patterns have been assigned as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), q (quartet), m (multiplet), br (broad), etc. Optical rotations were measured at 25 °C in indicated solvents. TLC plates were prepared using thin layers of silica gel on microscopic slides, and visualization of spots was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100−200 Mesh) using hexane and ethyl acetate as eluent.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-5-(1-(benzyloxy)allyl)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran (17).



Compound **15** (400 mg, 0.91 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. The solution was treated with commercially available vinylmagnesium bromide solution (1M in THF, 4.5 mL, 4.5 mmol) and the resulting solution was stirred for 1 h with gradual warming to room temperature. Saturated NH_4Cl (10 mL) was added carefully and the contents were extracted using EtOAc (3 × 15 mL). The combined extracts were dried and concentrated using rotary evaporator. The crude alcohol was used for the next step without further purification. R_f = 0.5 (hexane/EtOAc = 4:1). The crude alcohol was dissolved in dry DMF (5 mL) and NaH (47 mg, 1.5 mmol) was added to it at 0 °C. The mixture was stirred at the same temperature for 15 min and then benzyl bromide (0.12 mL, 1.2 mmol) was added dropwise to it. The solution was subsequently stirred at room temperature for 3 h and then quenched with ice and extracted with ether (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated in *vacuo* and the crude product was purified by silica gel chromatography to obtain **17** (296 mg, 58% over 2 steps) as a colourless oil: R_f = 0.6 (hexane/EtOAc = 9:1); IR (neat) ν_{max} 3526, 3100, 2824, 1450, 1427, 1347, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (1:0.31 mixture of isomers) δ 7.31 – 7.24 (m, 26H), 6.44 (s, 1H, minor isomer), 6.31 (s, 1H, major isomer), 5.81 (ddd, *J* = 10.3, 9.5, 3.1 Hz, 1H), 5.33 (ddd, *J* = 13.9, 11.7, 1.3 Hz, 2H), 5.16 – 5.03 (m, 1H), 4.76 – 4.71 (m, 2H), 4.65 – 4.57 (m, 2H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 5.3 Hz, 3H), 4.35 – 4.32 (m, 1H), 4.27 (dd, *J* = 11.5, 5.1 Hz, 2H), 4.05 (d, *J* = 2.9 Hz, 1H), 3.96 – 3.87 (m, 3H), 3.78 (ddd, *J* = 14.5, 11.0, 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.15, 138.96, 138.74, 138.29, 136.15, 128.69, 128.55, 128.52, 128.48, 128.44, 128.35, 128.17, 128.02, 127.90, 127.88, 127.77, 127.75, 127.68, 127.61, 127.51, 117.55, 112.47, 75.58, 73.67, 73.43, 72.86, 70.33, 68.17; HRMS calcd for $C_{37}H_{42}NO_5$ $[M + NH_4]^+$ 580.3063, Found: 580.3059.

2-(Benzyloxy)-2-((2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)ethanol (19).

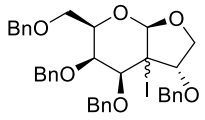


The diene **17** (500 mg, 0.89 mmol) was dissolved in acetone/^{t}BuOH/H_2O solvent system (3:1:1, 8 mL) and *N*-methylmorpholine *N*-oxide (120 mg, 1.04 mmol) followed by a catalytic amount of OsO_4 were added in succession and the resulting mixture was stirred at room temperature for 4 h. Then saturated $Na_2S_2O_5$ solution (8 mL) was added and the mixture stirred for 1 h. The compound was extracted using EtOAc (3 × 8 mL) and the combined extracts was dried (Na_2SO_4) and concentrated. The crude alcohol was cooled in THF/H_2O (4:1) mixture (10 mL) at 0 °C and sodium metaperiodate (557 mg, 2.60 mmol) was added to the vigorous stirred solution in portions over 1 h at same temperature followed by stirring for another 1 h. The reaction mixture was then filtered and the filtrate was extracted with CH_2Cl_2 (3 × 8 mL). Combined organic extracts was washed once with brine (1 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was dissolved in dry MeOH (8 mL) and cooled to 0 °C. Then, $NaBH_4$ (99 mg, 2.67 mmol) was added to the reaction mixture in portions over 5 min and stirring continued for 10 min. Subsequently, aq. NH_4Cl (10 mL) was added dropwise to the reaction mixture till the effervescence ceased. Extraction was done using CH_2Cl_2 (3 × 8 mL) and the

combined extracts was washed with brine (1 × 20 mL) and dried over Na_2SO_4. Removal of solvent under vacuum furnished a crude residue which was subjected to column chromatography to give **19** in 68% yield over the three steps (342 mg) as a thick liquid; R_f = 0.5 (hexane/EtOAc = 4:1); IR (neat) ν_{max}: 3379, 2976,1476, 1454, 1393, 1174, 1097 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 1:0.35 mixture of isomers): δ 7.37–7.20 (m, 20 H, both isomers), 6.48 (s, 1H, minor isomer), 6.38 (s, 1H, major isomer), 4.95–4.93 (m, 1H, major isomer), 4.80–4.78 (m, 1H, minor isomer), 4.72–4.44 (m, 7H, both isomers), 4.35–4.31(m, 1H, both isomer), 4.17–4.12(m, 1H, both isomer), 4.01–3.89 (m, 3H, both isomer), 3.85–3.83 (m, 1H, major isomer), 3.80–3.78(m, 1H, minor isomer), 3.69–3.54 (m, 2H, both isomers), 2.35 (br s, 1H, major isomer), 2.30 (br s, 1H, minor isomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.05, 143.74, 138.46, 138.37, 138.29, 138.15, 138.06, 137.91, 137.79, 128.65, 128.54, 128.48, 128.21, 128.06, 127.94, 127.91, 127.85, 127.78, 127.72, 127.43, 127.35, 127.23, 127.07, 109.09, 108.09, 79.41, 78.96, 75.61, 75.36, 74.38, 73.51, 73.48, 73.38, 72.97, 72.53, 72.07, 70.39, 70.04, 68.71, 67.96, 67.67, 66.01, 63.73; HRMS calcd for $C_{36}H_{39}O_6$ $[M + H]^+$ 567.2747, Found: 567.2749.

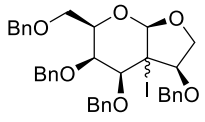
(3*S*,4*S*,5*S*,6*R*,7a*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-3a-iodohexahydro-2*H*-furo[2,3-*b*]pyran (20a) and (3*R*,4*S*,5*S*,6*R*,7a*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-3a-iodohexahydro-2*H*-furo[2,3-*b*]pyran (20b). *N*-Iodosuccinimide (238 mg, 1.059 mmol) was added to a solution of the primary alcohols **19** (400 mg, 0.706 mmol) in CH_2Cl_2 (40 mL) at room temperature and stirred for 1 h. It was then diluted with water (60 mL), extracted with CH_2Cl_2 (3 × 40 mL), washed with aq. $Na_2S_2O_3$ (5%) (1 × 40 mL) and brine (1 × 20 mL) and then dried over Na_2SO_4. The resulting residue was purified by column chromatography to yield a mixture of **20a** (99 mg, 20%) and **20b** (282 mg, 58%).

(3*S*,4*S*,5*S*,6*R*,7a*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-3a-iodohexahydro-2H-furo[2,3-*b*]pyran (20a).



R_f = 0.4 (hexane/EtOAc = 9:1); $[\alpha]_D^{25}$ = 25.3 (*c* 0.82, CH_2Cl_2); IR (neat) ν_{max}: 2930, 2851, 1471, 1427, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 20H), 5.53 (s, 1H), 4.83 – 4.79 (m, 3H), 4.53 (dd, *J* = 12.7, 7.4 Hz, 2H), 4.43 (dd, *J* = 11.5, 7.6 Hz, 2H), 4.27 – 4.21 (m, 2H), 4.16 (d, *J* = 3.5 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 1H), 3.91 (d, *J* = 3.5 Hz, 1H), 3.78 (dd, *J* = 8.5, 7.1 Hz, 1H), 3.67 (dd, *J* = 14.9, 6.6 Hz, 2H), 3.60 (dd, *J* = 7.9, 4.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.87, 138.13, 137.73, 137.37, 128.64, 128.58, 128.50, 128.36, 128.27, 128.19, 128.11, 127.98, 127.87, 127.66, 127.36, 109.28, 86.38, 79.68, 75.37, 74.70, 73.95, 73.80, 73.27, 72.85, 72.65, 68.09, 63.97; HRMS calcd for $C_{36}H_{38}IO_6$ $[M + H]^+$ 693.1713, Found: 693.1712.

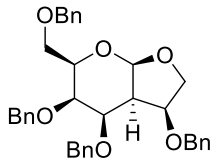
(3*R*,4*S*,5*S*,6*R*,7a*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-3a-iodohexahydro-2*H*-furo[2,3-*b*]pyran (20b).



R_f = 0.5 (hexane/EtOAc = 9:1); ; $[\alpha]_D^{25}$ = – 6.3 (*c* 0.55, CH_2Cl_2); IR (neat) ν_{max}: 3030, 2878, 1491, 1449, 1214, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 20H), 5.74 (s, 1H), 5.07 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.64 (dd, *J* = 41.6, 11.9 Hz, 2H), 4.58–4.42 (m, 4H), 4.09 (ddd, *J* = 12.5, 6.2, 2.0 Hz, 2H), 3.85 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.78 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.73 (dd, *J* = 9.4, 7.1 Hz, 1H), 3.65 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.41 (dd, *J* = 5.6, 3.4 Hz, 1H), 2.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.49, 138.00, 137.45, 137.17, 128.68,

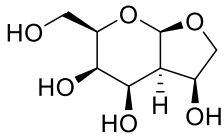
128.59, 128.50, 128.37, 128.34, 128.30, 128.20, 128.06, 128.04, 127.86, 127.68, 107.70, 80.36, 77.41, 77.16, 76.91, 76.42, 73.63, 73.57, 72.75, 71.71, 71.22, 70.01, 69.74, 68.40; HRMS calcd for $C_{36}H_{38}IO_6$ $[M + H]^+$ 693.1713, Found: 693.1710.

(3*S*,3a*S*,4*R*,5*R*,6*R*,7a*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)hexahydro-2*H*-furo[2,3-*b*]pyran (21).



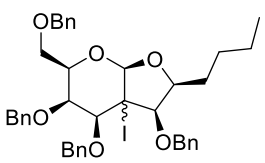
To a solution of **20b** (400 mg, 0.706 mmol) in ^{t}BuOH/ toluene (1:1 ratio; 10 mL) were added tributyltin chloride (0.038 mL, 0.141 mmol), AIBN (26 mg, 0.162 mmol) and $NaBH_3CN$ (89 mg, 1.412 mmol). The reaction mixture was then heated at 80 °C. After 1 h, solvent was removed *in vacuo*, and the residue was purified by column chromatography to give 186 mg (65%) of **21** as a colourless oil; R_f = 0.5 (hexane/EtOAc = 9:1); ; $[\alpha]_D^{25}$ = – 21.35 (*c* 0.85, CH_2Cl_2); IR (neat) ν_{max}: 2923, 2854, 1495, 1453, 1363, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.20 (m, 20H), 5.09 (d, *J* = 4.2 Hz, 1H), 4.87 (d, *J* = 11.8 Hz, 1H), 4.75–4.62 (m, 4H), 4.54 (dd, *J* = 12.5, 6.0 Hz, 2H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.19 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.12 (d, *J* = 3.0 Hz, 1H), 3.95 (ddd, *J* = 14.6, 7.8, 4.8 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 1H), 2.39 (dd, *J* = 11.0, 6.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.70, 138.07, 137.70, 128.65, 128.55, 128.45, 128.21, 128.14, 128.10, 127.90, 127.80, 101.51, 80.23, 77.41, 77.16, 76.91, 76.04, 74.30, 73.62, 71.18, 70.95, 70.81, 70.59, 69.41, 68.70, 43.72; HRMS calcd for $C_{36}H_{38}NaO_6$ $[M + Na]^+$ 589.2566, Found: 589.2565.

(3*S*,3a*S*,4*R*,5*R*,6*R*,7a*R*)-6-(Hydroxymethyl)hexahydro-2*H*-furo[2,3-*b*]pyran-3,4,5-triol (22).



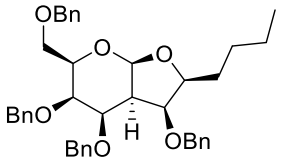
Compound **21** (50 mg, 0.088 mmol) was dissolved in dry CH_3OH (2.5 mL) and $Pd(OH)_2/C$ (10 mg, 20% w/w) was added to it. The mixture was stirred under 1 atm H_2 (balloon) for 4 h. The catalyst was filtered through a Celite® bed and washed with MeOH. The solvent was removed under vacuum and residue washed repeatedly with hexane. The compound was purified by washing with excess of 20% EtOAc/Hexane solution. Solvent was decanted and the residue left behind was dried under vacuum to afford **22** (15 mg, 81%) as a colorless oil; $[\alpha]_D^{25}$ = +1.6 (*c* 0.50, CH_3OH); IR (neat) ν_{max}: 3523, 3065, 2898, 1203, 1110 cm^{-1}; ^{1}H NMR (500 MHz, D_2O): δ 5.14 (d, *J* = 4.0 Hz, 1H, H-1), 4.41–4.39 (m, 1H, H-3), 4.38–4.34 (m, 1H, H-8), 4.07–4.05 (m, 2H, H-4, H-7), 3.7 –3.67 (m, 3H, H-5, H-6, H-7'), 3.49–3.47 (m, 1H, H-6), 2.66 (dt, *J* = 7.9, 4.7 Hz, 1H, H-2); ^{13}C NMR (125 MHz, D_2O): δ 100.31, 76.64, 73.83, 66.14, 63.97, 59.93, 47.18; HRMS calcd for $C_8H_{13}O_6$ $[M - H]^-$ 205.0712, Found: 205.0716.

(2*S*,3*R*,4*S*,5*S*,6*R*,7a*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-butyl-3a-iodohexahydro-2*H*-furo[2,3-*b*]pyran (23).



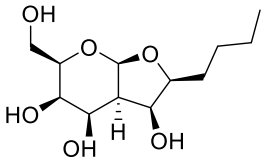
The aldehyde **18b** (400 mg, 0.708 mmol) was dissolved in dry THF (10 mL) and cooled to -30 °C. The solution was treated with excess of freshly prepared *n*-butylmagnesium bromide and the resulting solution was stirred 1 h with gradual warming to room temperature. Saturated NH_4Cl (20 mL) was carefully added and the contents were extracted using EtOAc (3 × 15 mL). The combined extracts were dried and concentrated using rotary evaporator and the residue was subjected to the next step. The Crude alcohol was subjected to iodocyclization with NIS in the manner as was done for **20a/b**, to yield 389 mg (73.3%) of **23** as a colourless oil; R_f = 0.5(hexane/EtOAc = 9:1); ; $[\alpha]_D^{25}$ = +26.0 (*c* 0.35, CH_2Cl_2); IR (neat) ν_{max}: 3092, 2826, 1450, 1369, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–6.90 (m, 20H), 5.58 (s, 1H), 4.81 (dt, *J* = 20.9, 8.2 Hz, 4H), 4.59–4.43 (m, 3H), 4.37–4.25 (m, 3H), 4.18 (d, *J* = 3.5 Hz, 1H), 3.91 (d, *J* = 3.5 Hz, 1H), 3.63–3.57 (m, 1H), 1.74 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.62–1.14 (m, 6H), 0.83 (t, *J* =7.45 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.96, 138.23, 137.72, 137.30, 128.57, 128.52, 128.42, 128.19, 128.12, 128.03, 127.98, 127.85, 127.60, 127.13, 107.01, 86.83, 81.64, 79.32, 75.14, 74.60, 73.87, 73.72, 72.70, 72.59, 68.04, 65.44, 30.68, 28.80, 22.74, 14.10; HRMS calcd for $C_{40}H_{45}INaO_6$ $[M + Na]^+$ 771.2159, Found: 771.2161.

***(2S,3S,3aS,4R,5R,6R,7aR*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-butylhexa- hydro-2*H*-furo[2,3-*b*]pyran (24).**



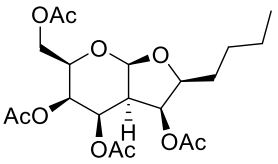
Deiodination of compound **23** (250 mg, 0.334 mmol) was performed in the manner as was done for **21**, to yield 150 mg (72%) of **24** as a colourless oil; R_f = 0.5 (hexane/EtOAc = 9:1); ; $[\alpha]_D^{25}$ = – 21.35 (*c* 0.85, CH_2Cl_2); IR (neat) ν_{max}: 2923, 2854, 1495, 1453, 1363, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 20H), 5.20 (d, *J* = 4.4 Hz, 1H), 4.97 (d, *J* = 11.3 Hz, 1H), 4.72 (d, *J* = 5.4 Hz, 2H), 4.64 – 4.58 (m, 3H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 9.7 Hz, 1H), 4.38 – 4.29 (m, 2H), 3.94 (d, J = 2.8 Hz, 1H), 3.81 (dd, J = 6.7, 2.9 Hz, 1H), 3.71 – 3.64 (m, 1H), 3.58 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.50 (dd, *J* = 7.7, 5.3 Hz, 1H), 2.75 (dd, *J* = 11.1, 4.8 Hz, 1H), 1.63–1.59 (m, 2H), 1.33–1.25 (m, 4H), 0.84 (t, *J* = 8.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.92, 138.00, 128.60, 128.55, 128.43, 128.39, 128.32, 128.23, 128.19, 128.03, 127.90, 127.70, 127.62, 127.53, 95.83, 75.17, 74.60, 73.70, 72.86, 71.69, 71.31, 71.19, 70.75, 70.56, 69.06, 38.71, 35.51, 27.15, 22.93, 14.19; HRMS calcd for $C_{40}H_{46}NaO_6$ $[M + Na]^+$ 645.3192, Found: 645.3188.

(2*S*,3*S*,3a*R*,4*R*,5*R*,6*R*,7a*R*)-2-Butyl-6-(hydroxymethyl)hexahydro-2*H*-furo[2,3-*b*]pyran-3,4,5-triol (25).



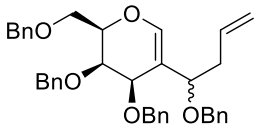
Deprotection of bezyl group of the compound **24** (50 mg, 0.088 mmol) was performed in the manner as was done for **22**, to yield 15 mg (81%) of **25** as a colorless oil; $[\alpha]_D^{25}$ = +33.3 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, D_2O): δ 5.13 (d, *J* = 4.3 Hz, 1H), 4.58 (t, *J* = 5.8 Hz, 1H), 4.30–4.18 (m, 1H), 4.01 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.70 (d, *J* = 3.5 Hz, 1H), 3.66–3.52 (m, 2H), 3.44–3.31 (m, 1H), 2.36 (dd, *J* = 11.8, 5.1 Hz, 1H), 1.58–1.35 (m, 2H), 1.35–1.10 (m, 4H), 0.75 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, D_2O): δ 99.52, 82.20, 74.04, 70.78, 67.07, 66.93, 61.24, 52.81, 28.08, 27.77, 22.07, 13.22; HRMS calcd for $C_{12}H_{21}O_6$ $[M-H]^-$ 261.1338, Found: 261.1336.

(2*S*,3*S*,3a*S*,4*R*,5*R*,6*R*,7a*R*)-6-(Acetoxymethyl)-2-butylhexahydro-2*H*-furo[2,3-*b*]pyran-3,4,5-triyl triacetate (26).



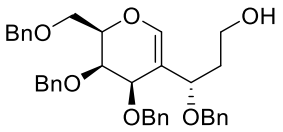
The alcohol **25** (15 mg, 0.057 mmol) was stirred with at room temperature in acetic anhydride - Et_3N mixture (1:1, 2 mL) in presence of catalytic amount of DMAP, for 6 h following which solvent was evaporated and residue was purified by column chromatography to afford **26 (**18 mg, 71%) as colorless oil; R_f = 0.5 (hexane/EtOAc = 3:1); IR (neat) ν_{max}: 2958, 1744, 1597, 1371, 1239, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.02 (t, *J* = 6.8 Hz, 1H, H-8), 5.33–5.15 (m, 3H, H-1, H-3, H-4), 4.52 (ddd, *J* = 8.8, 7.2, 4.2 Hz, 1H, H-7), 4.17–4.05 (m, 2H, H-6, H-6'), 3.79 (t, *J* = 6.6 Hz, 1H, H-5), 2.74 (td, *J* = 6.7, 4.1 Hz, 1H, H-2), 2.18 (s, 3H), 2.03 (s, 6H), 1.95 (s, 3H), 1.55–1.19 (m, 6H), 0.90 (t, *J* = 6.85 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.56, 170.22, 169.73, 169.66, 99.37, 80.34, 72.50, 70.11, 67.37, 65.40, 62.11, 47.78, 29.11, 20.85, 20.78, 20.67, 20.58; HRMS calcd for $C_{20}H_{34}NO_{10}$ $[M + NH_4]^+$ 448.2183, Found: 448.2189.

(2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-5-(1-(benzyloxy)but-3-en-1-yl)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran (27).



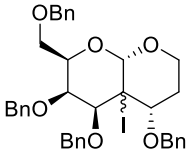
The aldehyde **15** (350 mg, 1.05 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. The solution was treated with freshly prepared excess allylmagnesium chloride and the resulting solution was stirred 1 h with gradual warming to room temperature. Saturated NH_4Cl (10 mL) was added carefully and the contents were extracted using EtOAc (3 × 15 mL). The extracts were dried and concentrated using rotary evaporator. The crude compound was used for the next step without further purification. R_f = 0.5 (hexane/EtOAc = 4:1). The crude alcohol was dissolved in dry DMF (5 mL) and NaH (47 mg, 1.5 mmol) was added at 0 °C. The mixture was stirred at same temperature for 15 min and then benzyl bromide (0.12 mL, 1.2 mmol) was added dropwise to it. The solution was stirred at room temperature for 3 h and then quenched with ice and extraction was done with ether (3 × 5 mL). The extracts were dried over Na_2SO_4 and concentrated in *vacuo* and the crude was purified by silica gel chromatography to obtain **27** (309 mg, 68% over 2 steps) as a colourless oil: R_f = 0.5 (hexane/EtOAc = 9:1); $[\alpha]_D^{25}$ = -47.1 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 3508, 3071, 2930, 2858, 1598, 1472, 1427, 1347, 1161, 1111 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$, 1:0.9 mixture of isomers) δ 7.37 – 7.14 (m, 20H, both isomers), 6.31 (s, 1H, minor isomer), 6.30 (s, 1H, major isomer), 5.83 – 5.61 (m, 1H, both isomers), 5.14 – 4.92 (m, 2H, both isomers), 4.86 – 4.38 (m, 8H, both isomers), 4.31 – 4.22 (m, 1H, both isomers), 4.12 (br s, 1H, both isomers), 4.06 – 3.71 (m, 4H, both isomers), 2.51 – 2.38 (m, 2H, both isomers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.33, 142.88, 142.42, 142.00, 141.60, 140.53, 138.86, 138.71, 138.26, 138.11, 136.78, 135.63, 135.18, 132.94, 130.53, 129.85, 128.56, 128.50, 128.44, 128.40, 128.30, 128.23, 128.03, 127.94, 127.82, 127.73, 127.49, 127.37, 127.17, 126.94, 126.45, 126.32, 120.98, 116.62, 116.55, 110.99, 110.86, 108.98, 78.48, 77.81, 75.54, 73.77, 73.56, 73.47, 72.98, 72.52, 70.58, 69.96, 69.71, 69.44, 68.22, 67.96, 40.18, 38.79; HRMS calcd for $C_{38}H_{44}NO_5$ $[M + NH_4]^+$ 594.3219, Found: 594.3216.

(*S*)-3-(Benzyloxy)-3-((2*R*,3*R*,4*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2*H*-pyran-5-yl)propan-1-ol (28a).



The diene **27** (500 mg, 0.868 mmol) was dissolved in acetone/^{t}BuOH/H_2O solvent system (3:1:1,8 mL) and *N*-methyl morpholine *N*-oxide (120 mg, 1.04 mmol) followed by catalytic amount of OsO_4 were added in succession and the resulting mixture was stirred at room temperature for 4 h. Then saturated $Na_2S_2O_5$ solution (8 mL) was added and the mixture stirred for 1 h. The compound was extracted using EtOAc (3 × 8 mL) and the extracts were dried (Na_2SO_4) and concentrated. The crude alcohol was cooled in THF/H_2O (4:1) mixture (10 mL) at 0 °C and sodium metaperiodate (557 mg, 2.60 mmol) was added to the vigorous stirred solution in portions over 1 h at same temperature followed by stirring for another 1 h. The reaction mixture was then filtered and the filtrate was extracted with CH_2Cl_2 (3 × 8 mL). Combined organic extracts were washed once with brine (1 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was dissolved in dry MeOH (8 mL) and cooled to 0 °C. Then, $NaBH_4$ (98 mg, 2.60 mmol) was added to the reaction mixture in portions over 5 min and stirring continued for 10 min. Subsequently, aq. NH_4Cl (10 mL) was added drop wise to the reaction mixture till the effervescence ceased. Extraction was done using CH_2Cl_2 (3 × 8 mL) and extracts were washed with brine (1 × 20 mL) and dried over Na_2SO_4.The removal of solvent under vacuum furnished a crude residue, which was separable by column chromatography to give **28a** (190 mg, and other isomer **28b,** 171 mg, combined yield 72% over 3 steps) as colourless oil: R_f = 0.5 (hexane/EtOAc = 4:1); $[\alpha]_D^{25}$ = -30.0 (*c* 1.20, CH_2Cl_2); IR (neat) $\nu_{max,}$ 3467, 2923, 2867,1493, 1450, 1089, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 20H), 6.35 (s, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.69 (dd, *J* = 31.1, 11.8 Hz, 2H), 4.54 (t, *J* = 11.1 Hz, 2H), 4.48 – 4.36 (m, 3H), 4.27 (d, *J* = 11.9 Hz, 1H), 4.12 (d, *J* = 3.1 Hz, 1H), 3.92 (ddd, *J* = 13.0, 11.3, 6.5 Hz, 3H), 3.79 (dd, *J* = 11.1, 2.6 Hz, 1H), 3.59 (t, *J* = 5.4 Hz, 2H), 2.26 (s, 1H), 1.95 (td, *J* = 14.3, 6.1 Hz, 1H), 1.76 (dq, *J* = 15.2, 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.85, 139.26, 138.86, 138.64, 138.26, 128.59, 128.55, 128.50, 128.20, 128.17, 128.09, 127.90, 127.75, 127.50, 127.45, 127.33, 127.19, 126.70, 96.57, 77.70, 75.68, 75.61, 75.25, 75.01, 73.49, 72.85, 71.19, 70.90, 70.47, 41.57, 35.70; HRMS calcd for $C_{37}H_{40}NaO_6$ $[M + Na]^+$ 603.2723, Found: 603.2726.

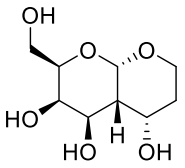
(2*R*,3*S*,4*S*,5*S*,8a*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-4a-iodooctahydropyrano[2,3-*b*]pyran (29).



N-iodosuccinimide (58 mg, 0.259 mmol) was added to a solution of **28a** (100 mg, 0.172 mmol) at room temperature and stirred for 15 min, diluted with water (10 mL), extracted with CH_2Cl_2 (3 × 8 mL), washed with aq. $Na_2S_2O_3$ (5%) (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4. The crude residue was subjected to column chromatography to give **29** (103 mg, 85%) as a colourless oil: R_f = 0.6 (hexane/EtOAc = 9:1); $[\alpha]_D^{25}$ = – 12.1 (*c* 0.85, CH_2Cl_2); IR (neat) $\nu_{max,}$ 2924, 2867, 1450, 1369, 1066, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 6.96 (m, 20H), 5.14 (s, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.77 (s, 2H), 4.61– 4.51 (m, 4H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.09 – 4.00 (m, 1H), 3.96 – 3.87 (m, 2H), 3.84 – 3.74 (m, 3H), 3.68 (dd, *J* = 8.6, 5.2 Hz, 1H), 3.56 (dd, *J* = 10.8, 4.7

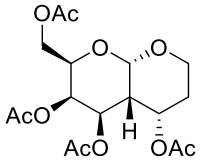
Hz, 1H), 1.96 – 1.86 (m, 1H) 1.63 – 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.50, 138.06, 137.75, 137.71, 128.60, 128.41, 128.32, 128.23, 128.09, 128.04, 127.98, 127.91, 127.84, 127.27, 126.82, 103.21, 89.70, 75.50, 75.44, 75.11, 74.28, 73.79, 70.91, 68.10, 64.29, 61.35, 31.75; HRMS calcd for $C_{37}H_{43}INO_6$ $[M + NH_4]^+$ 724.2135, Found: 724.2141.

(2*R*,3*R*,4*R*,4a*S*,5*S*,8a*S*)-2-(Hydroxymethyl)octahydropyrano[2,3-*b*]pyran-3,4,5-triol (31).



To a solution of **29** (150 mg, 0.212 mmol) in ^{t}BuOH/ toluene (1:1 ratio; 4 mL) were added tributyltin chloride (0.012 mL, 0.042 mmol), AIBN (8 mg, 0.049 mmol) and $NaBH_3CN$ (28 mg, 0.424 mmol). The reaction mixture was then heated at 80 °C. After 2 h, solvent was removed *in vacuo*, and the residue was purified by column chromatography to give **30** (94 mg, 76%) which was dissolved in dry CH_3OH (3 mL) and $Pd(OH)_2/C$ (19 mg, 20% w/w) was added. The mixture was stirred under 1 atm H_2 (balloon) for 4 h. The catalyst was filtered through a Celite® bed and washed with MeOH. The solvent was removed under vacuum and residue washed repeatedly with hexane. The compound was purified by washing with excess of 20% EtOAc/Hexane solution. The solvent was decanted and the residue left behind was dried under vacuum to afford **31** (32 mg, 88%) as a pale yellow liquid: $[\alpha]_D^{25}$ = -2.2 (*c* 0.11, CH_3OH); IR (neat) ν_{max}: 3349, 3062, 1237, 1100, 1028 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.74 (d, *J* = 2.3 Hz, 1H), 4.14 – 4.02 (m, 3H), 3.74 – 3.57 (m, 4H), 3.52 – 3.45 (m, 1H), 2.27 – 2.18 (m, 1H), 1.85 (ddd, *J* = 14.6, 4.8, 2.5 Hz, 1H), 1.74 – 1.62 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 94.16, 74.83, 66.83, 63.50, 58.95, 57.07, 54.68, 40.42, 28.90; HRMS calcd for $C_9H_{15}O_6$ $[M-H]^-$ 219.0863, Found: 218.0863.

(2*R*,3*R*,4*R*,4a*S*,5*S*,8a*S*)-2-(Acetoxymethyl)octahydropyrano[2,3-*b*]pyran-3,4,5-triyl triacetate (32).



Compound **31** (24 mg, 0.109 mmol) was stirred at room temperature in acetic anhydride-Et_3N mixture (1:1, 2 mL) for 12 h following which solvent was evaporated and residue was purified by column chromatography to afford 36 mg (85%) of acetate **32** as a pale yellow liquid: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{25}$ = +9.5 (*c* 0.20, CH_2Cl_2); IR (neat) ν_{max}: 3062, 3029, 2860, 1739, 1453, 1237, 1100, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (t, *J* = 3.5 Hz, 1H, H-3), 5.15 (dd, *J* = 6.2, 3.5 Hz, 1H, H-4), 5.13 – 5.07 (m, 1H, H-7), 4.83 (d, *J* = 3.5 Hz, 1H, H-1), 4.79 – 4.70 (m, 1H, H-6)), 4.50 (dd, *J* = 11.9, 3.3 Hz, 1H, H-6'), 4.21 (ddd, *J* = 9.1, 6.2, 3.2 Hz, 1H, H-5), 4.14 (ddd, *J* = 12.1, 4.9, 2.8 Hz, 1H, H-9), 3.45 (td, *J* = 11.9, 2.4 Hz, 1H, H-9'), 2.58 – 2.54 (m, 1H, H-2), 2.15 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.92 (dd, *J* = 12.7, 5.0 Hz, 1H, H-8), 1.75 – 1.71 (m, 1H, H-8'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.21, 170.33, 169.73, 169.69, 95.68, 71.73, 67.41, 64.76, 64.59, 39.10, 29.81, 28.22, 21.49, 21.21, 21.15, 20.83; HRMS calcd for $C_{17}H_{24}NaO10_{10}$ $[M + Na]^+$ 411.1267, Found: 411.1261.

General procedure for enzyme inhibition studies

All the enzymes and their corresponding substrates were procured from Sigma-Aldrich Chemical Co. The inhibition studies of compounds (**22**, **25** and **31**) were determined by measuring residual hydrolytic activities of the glycosidases. The substrates and enzymes were prepared as 0.025 M solutions in the respective pH buffer

solutions of the corresponding enzyme. In all cases, the substrates used were the corresponding *p*-nitrophenyl glycopyranosides. The incubation mixture consisted of 100 µL of enzyme solution, 200 µL of 1 mg mL−1 aqueous solution of the test compound, and 100 µL of the appropriate buffer solution of the optimum pH for the enzyme. After incubation at 37 °C for 1 h, 100 µL of the substrate solution was added and allowed to react for 10 min. The reaction mixture was quenched using 2.5 mL of 0.05 M borate buffer (pH = 9.8). In all cases, control experiments were run simultaneously in the absence of test compound. A series of blank experiments for the substrate were also carried out in the respective buffer solutions without the enzyme or test compounds. The absorbance of the liberated *p*-nitrophenol in each reaction (both test and control reactions) was recorded using spectrophotometer at 405 nm. Percentage inhibition was calculated as the ratio of the difference in the observed absorbances of the control and test reactions to the observed absorbance of the control reaction. Results have thus been reported as IC_{50} values, which is the concentration of the test compound that causes 50% inhibition of the enzyme.

Acknowledgements

We are thankful to the DST, New Delhi for the J. C. Bose Fellowship to Y. D. V. (grant number JCB/SR/S2/JCB-26/2010). P. R. thanks to the University Grant Commission, New Delhi, for Senior Research Fellowship, and C. A. thanks to the Council of Scientific Industrial Research, New Delhi, for Senior Research Fellowship.

Supplementary Material

Copies of ^{1}H NMR, ^{13}C NMR and 2D NMR spectra of new compounds are given in the Supplementary Material file associated with the manuscript.

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