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Regioselective facile synthesis of novel isoxazole-linked glycoconjugates†

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A concise and efficacious protocol for the regioselective synthesis of novel 3,5-disubstituted isoxazole-linked glycoconjugates (**4**, **7** and **9**) *via* a 1,3-dipolar cycloaddition reaction between *in situ* generated glycosyl-β-nitrile oxide (derived from glycosyl-β-nitromethane ester **3** and **6**) and various terminal alkynes bearing sugar, alkyl and aryl substituents (**2a–n**), has been devised. The formation of nitrile oxide during the reaction course has been supported by DFT calculations, which gave the optimized structure of the glycosyl-β-nitrile oxide ester. This one-pot methodology offers a way for utilizing D-glucose derived nitrile oxide, as a new variant in click chemistry for the synthesis of novel isoxazole-linked glycoconjugates, paving a new route for the construction of carbohydrate based scaffolds of multifaceted biological profiles.

Introduction

Isoxazoles constitute an important class of five-membered heterocycles employed in a wide range of pharmaceutical activities including, antitumor,[1,2] anticancer,[3] antitubercular,[4] antibactericidal[5] and antifungicidal.[6] They are important constituents of various drugs such as COX-2 selective inhibitor Valdecoxib (**I**),[7] anti-rheumatic Leflunomide (**II**),[8] β-lactamase-resistant Cloxacillin (**III**),[9] androgenic steroid Danazol (**IV**)[10] (Fig. 1). The immense bio-activity of the isoxazole ring may be attributed to the facile cleavage of the N–O bond, which leads to the formation of other more reactive species. Because of their versatility towards chemical transformations to useful intermediates involved in various natural product syntheses, substituted isoxazoles are considered to be important synthons.[11]

Considering the pivotal role of carbohydrates in various physiological and pathological important processes,[12] there has been a rapid growth of interest in the synthesis of novel glycoconjugates. In this context 'bioconjugation' has emerged as a simple and fast growing strategy for the formation of novel conjugates possessing the combined properties of parent components.[13–15] Due to cooperative action of both the entirely distinct entities in the new conjugate, they are known to exhibit unusual pharmacological activities.[16–19] The 1,2,3-triazole linker formed conveniently by 'click chemistry'[20] is widely utilized for conjugating two different entities to form new conjugates.[19] In the similar way, the isoxazole ring may also be used as a linker for bioconjugation.

The nitroalkanes are sufficiently stable and can easily be transformed to stable nitrile oxide by various methods.[21] Due to the significant role of carbohydrates in cycloaddition reactions,[22] we envisaged to employ the isoxazole moiety in the aforementioned sense. Herein, we report a highly regioselective facile synthesis of novel 3,5-disubstituted isoxazole-linked glycoconjugates utilizing [3 + 2] cycloaddition between glycosyl-β-nitrile oxide ester and various substituted terminal alkynes. The methodology is advantageous as it provides an expeditious and simple route for the introduction of isoxazole-ring at different positions of sugar derivatives, with apparent ease. Hence, it may prove as a promising strategy in the field of carbohydrate chemistry for the targeted synthesis of complex isoxazole-linked glycoconjugates.

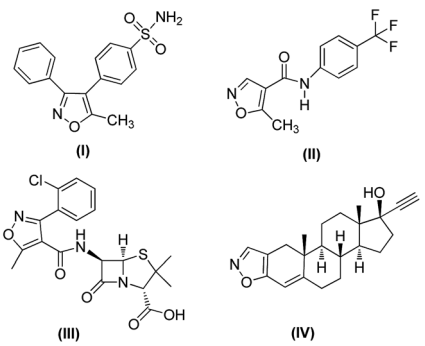

Fig. 1 Structure of some isoxazole based drugs.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR for all the new compounds, single crystal X-ray data of **9a** and computational data has been provided. CCDC 1042109. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra05905d

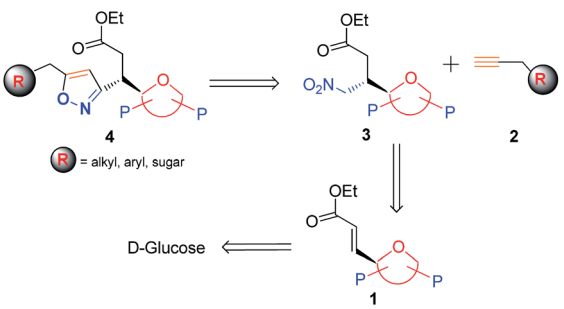
Results and discussion

Towards our target molecule isoxazole-linked glycoconjugate **4**, a retrosynthetic analysis was carried out by taking into account the ready access to alkyne **2**, and glycosyl-β-nitromethane ester **3** prepared from corresponding glycosyl-β-olefinic ester **1** (Scheme 1).

The synthetic phase of our investigation started from cheap and readily available D-glucose, which after processing through a number of high-yielding steps, such as isopropylidene protection, 3-*O*-benzyl protection, selective 5,6-isopropylidene deprotection, followed by $NaIO_4$ oxidation and finally HEW-Wittig olefination afforded glycosyl olefinic ester (1*R*,2*R*,3*S*,4*R*)-ethyl-[3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-gluco]-heptfuran-5-enuronate **1**.[23] Further reaction of compound **1** (1.0 equiv) with nitromethane (2.2 equiv) in presence of K_2CO_3 (2.73 equiv) at refluxing temperature for 6 h in anhydrous ethanol furnished (1*R*,2*R*,3*S*,4*R*,5*R*)-ethyl-[3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-nitromethyl]-β-L-idoheptofuranurnate **3** (ref. 24) in 85% yield (Scheme 2).

After this, we focused our attention towards the generation of substituted isoxazole ring at the C-5 position of glycosyl olefinic ester **1**. For this purpose, corresponding nitrile oxide from compound **3** has to be generated which can undergo [3 + 2] dipolar cycloaddition with diverse alkynes (Scheme 3). The synthesis of various sugar alkynes is required for this step, which was done by utilizing a variety of readily available monosaccharides (D-glucose, D-mannose, D-ribose, D-galactose and D-fructose). All these monosaccharides after processing through suitable protection strategies[25,26] were converted to their respective sugar alcohols, which on NaH mediated reaction of propargyl bromide in anhydrous DMF afforded corresponding *O*-propargyl ethers **2a–i** in good to excellent yield.[27,28] Hence, the treatment of methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside with NaH and propargyl bromide in dry DMF at 0 °C for 12 h led to the formation of methyl-2,3-*O*-isopropylidene-5-*O*-propargyl-β-D-ribofuranoside **2a** in 84% yield (see, ESI Table S1†).

The developed alkynes **2a–i** were further treated with glycosyl-β-nitromethane ester **3** in presence of phenyl isocyanate and triethylamine in dry toluene at room temperature under Mukaiyama's condition.[21a] The reaction proceeded with complete regioselectivity affording the 3,5-disubstituted



Scheme 2 Synthesis of glycosyl-β-nitromethane ester **3**.

isoxazole-linked glycoconjugates in 32–42% yield after purification by column chromatography over silica gel (Scheme 4).

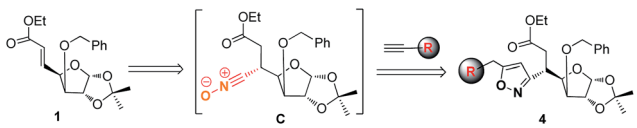
The low yield might be due to the formation of furoxane, urea, and CO_2 as side product under this condition.[21a] Moreover, the Mukaiyama method states for such reactions to occur *via* the generation of nitrile oxide, therefore, a substantial increase in nitrile oxide generated during the course of reaction would led to an enhanced yield of products. Thus, in order to access the yield further, we investigated the one-pot reaction of compound **3** with alkynes **2** using tosyl chloride, 18-crown-6 ether system, and organic/inorganic bases[21c] in dry toluene at 80 °C to afford 3,5-disubstituted isoxazoles **4** in good yields. This methodology also performed well under MW irradiation at 100 W and 110 °C for 15–20 minutes. The short reaction time with enhanced yield, simple work-up procedure, and easy separation of isoxazoles (soluble in toluene) from solid by-products (water soluble) makes this strategy more advantageous (Scheme 5).

We briefly investigated the effect of diverse bases, results summarized in Table 1. The reactions carried out using 2.0 equiv of either bicarbonate or carbonate bases demonstrated a greater yield of products (entry 1–3). In case of amine bases, low yield of product was obtained (entry 4–9, Table 1). Using K_2CO_3 as base the reaction was accomplished in significantly less time with higher yield of product (entry 2, Table 1).

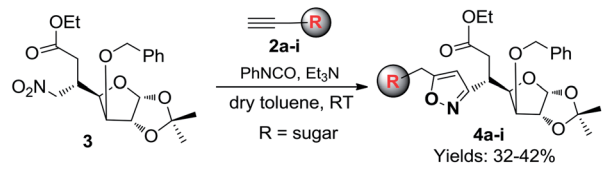
Next, the reaction was screened for a variety of organic solvents in presence of 18-crown-6 (10 mol%), K_2CO_3 (2.0 equiv) and TsCl (1.3 equiv) at 80 °C. The results clearly illustrated that the reaction proceeded best in nonpolar solvents such as toluene and benzene and the product was isolated in good yield and short reaction period. When methanol was used as solvent, the product was obtained only in trace amount even after stirring the reaction for 20 hours. The reaction showed poor performance in tetrahydrofuran, acetone, 1,4-dioxane, diethyl ether, acetonitrile, dichloromethane and chloroform in terms of yield and reaction time. The yield could not improve even when the reaction was stirred for longer durations (see, ESI Table S2†).

The final optimization study was done by observing the effect of crown ethers as catalyst for the reaction. The reaction was screened under the above conditions with 18-crown-6 ether and monaza-15-crown-5 anellated to methyl-4,6-*O*-benzylidene-α-D-

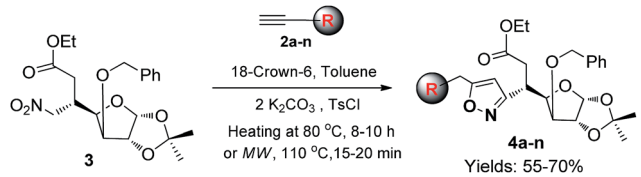
Scheme 1 Retrosynthetic analysis.



Scheme 3 Formation of isoxazole ring at C-5 position of compound **1**.

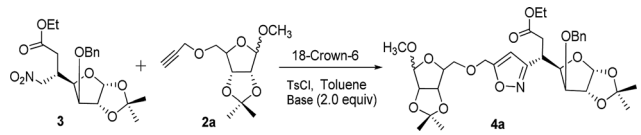


Scheme 4 Synthesis of isoxazole-linked glycoconjugates by Mukaiyama's method.



Scheme 5 Synthesis of isoxazole-linked glycoconjugates.

Table 1 Base optimization using TsCl (1.3 equiv) and 18-crown-6 (10 mol%) in anhydrous toluene with alkyne **2a** (1.2 equiv) and **3** (1.0 equiv)



Entry	Base	Time[a]	Yield[b] (%)
1	Na_2CO_3	8	65
2	K_2CO_3	8	70
3	$NaHCO_3$	8	64
4	DMAP	18	12
5	DIPEA	18	10
6	DBU	18	10
7	DABCO	14	5
8	Et_3N	14	20
9	Pyridine	18	10

[a] Reaction time in hours. [b] Isolated yield of product **4a**.

gluco pyranoside.[29,30] The obtained results suggested that 18-crown-6 ether was better in terms of yield as compared to uncatalyzed reaction and monaza-15-crown-5 ether. This might be due to the cavity size of 18-crown-6 ether which is most suitable for potassium ions, having a binding constant of 10^6 M^{-1} in methanol for K^+ ions.[31] In case of 15-crown-5 ethers, the cavity size is decreased and is not so appropriate for binding large ions like potassium[32] (Table 2).

Finally, the catalyst amount was optimized and it was observed that 10 mol% of 18-crown-6 gave the best yield of product. However, the yield did not improved with temperature rise in presence of same amount of catalyst (10 mol%) (entry 2–3, Table 3). No enhancement in yield was noticed on increasing the mol% of catalyst (entry 4–10, Table 3). Hence, it can be concluded that 10 mol% of 18-crown-6 at 80 °C gave the maximum product yield. These observations suggested that the crown catalyst might be catalyzing the reaction by enhancing the rate of formation of *O*-tosylnitronate (refer mechanism; Fig. 6), by weakening the interaction between potassium ion and glycosyl-β-nitronate moiety and hence facilitating the attack of tosyl group (Fig. 2).

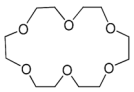
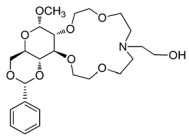
Thus, under the above optimized reaction conditions, the model reaction between glycosyl-β-nitromethane ester **3** and methyl-2,3-*O*-isopropylidene-5-*O*-propargyl-β-D-ribofuranoside **2a** gave regioselectively the desired 3-[ethyl-(3′-*O*-benzyl-5′,6′-dideoxy -1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(methyl-2″,3″-*O*-isopropylidene-5″-*O*-methyl-β-D-ribofuranoside-5″-yl)-isoxazole **4a** (70% yield). The regioisomeric nature of compound **4a** was established based on its spectroscopic data. In ^{1}H NMR spectrum of **4a**, the appearance of characteristic singlet at δ 6.26 for the proton of the isoxazole ring confirms the formation of cycloadduct. Other signals such as a multiplet integrated to five protons at δ 7.33 and the two anomeric protons appeared at δ 5.91 ($J = 3.6$ Hz) as a doublet (1-*H*″), δ 4.94 as singlet (1-*H*′) and the remaining signals are in accordance with the assigned structure of glycoconjugated isoxazole. In the ^{13}C NMR, the signals at δ 167.9, 163.8 and 104.1 ppm were attributed for the carbon of isoxazole ring. The carbonyl carbon appeared at δ 170.9 and the two anomeric carbons appeared at δ 109.1 and 104.7, which lent further support to the assigned structure of desired cycloadduct. The IR spectrum showed absorption bands corresponding to –C–O–N– (1212 cm^{-1}) and C=N (1608 cm^{-1}) functional groups respectively. A molecular ion peak at m/z 634 $[M + H]^+$ in mass spectrum finally confirmed the unambiguous structure of compound **4a**.

The stereochemical outcome of the regioselective cycloaddition and the configuration of the synthesized isoxazole ring can be well predicted on the basis of the configuration of glycosyl-β-nitromethane ester **3**. Based on Felkin-Anh and Cram's transition state it can be well predicted, that the major attack of nitromethane at C-5 in olefinic ester would take place from the side of the least bulky group (hydrogen attached to C-4 of the furanose ring, the "*Si*" diastereoface), and hence the major reaction product has "*R*" configuration at C-5, while that of the minor one is '*S*'.[23a,b] According to literature precedent, the conjugate addition of nitromethane on glycosyl-β-olefinic ester **1** gave almost exclusively the β-L-ido isomer having '*R*' configuration at C-5.[24] So, the synthesized glycoconjugates with the isoxazole ring at the C-5 carbon, would also be the β-L-ido isomer *i.e.* the isoxazole ring would be below the plane with respect to glycosyl-β-olefinic ester (Scheme 6).

Having established the reaction conditions for the regioselective formation of 3,5-disubstituted isoxazole-linked glycoconjugate **4a** by reaction of *O*-propargyl ether of sugar **2a** and glycosyl-β-nitromethane ester **3**, we further explored the scope of other alkynes in this reaction and developed a library of isoxazole-linked glycoconjugate **4a–n** in good yields (Table 4). Reaction yield was comparatively better in case of *O*-propargyl ethers of sugar (entry 1–9, Table 4). The methodology displays good compatibility with a variety of terminal alkynes having sugar, alkyl and aryl functionalities.

The methodology was further explored with glycosyl-β-olefinic ester derivative having 3-*O*-ethyl substituent at the C-3

Table 2 Catalyst optimization with compound **3** and **2a** using TsCl (1.3 equiv) and K_2CO_3 (2.0 equiv) in dry toluene

Entry	Catalyst	Mol%	Temp.[a] (°C)	Time[b] t_1 (h)/t_2 (min)	Yield[c] (%) y_1/y_2
1		30	80	8/15	68/70
2		30	100	10/20	42/45
3	No catalyst	—	80	8/20	42/45

[a] Reaction temperature 80–100 °C. [b] Time: t_1 = reaction under heating, t_2 = reaction under MW at 110 °C with a stirring rate 200 rpm. [c] Isolated yield of glycoconjugate **4a**: y_1 = yield under heating condition, y_2 = yield under MW condition.

Table 3 Catalyst (18-crown-6) amount optimization study using TsCl (1.3 molar equiv) and K_2CO_3 (2.0 molar equiv) in dry toluene with alkyne **2a** (1.2 equiv) and compound **3** (1.0 equiv)

Entry	[a]Mol%	Temp (°C)	Time[b] t_1 (h)/t_2 (min)	Yield[c] (%) y_1/y_2
1	5	100	8/15	65/66
2	**10**	**80**	**8/15**	**69/70**
3	10	100	8/15	69/70
4	15	80	10/20	68/69
5	20	100	8/15	67/68
6	25	80	8/15	66/66
7	30	80	8/15	68/70
8	35	80	10/20	65/66
9	40	100	10/20	63/65
10	50	80	10/20	65/66

[a] Mol% of 18-crown-6 catalyst. [b] Reaction time: t_1 = reaction under heating, t_2 = reaction under microwave at 110 °C with a stirring rate 200 rpm. [c] Isolated yield of product isoxazole-linked glycoconjugates **4a**: y_1 = yield under heating condition, y_2 = yield under microwave condition.

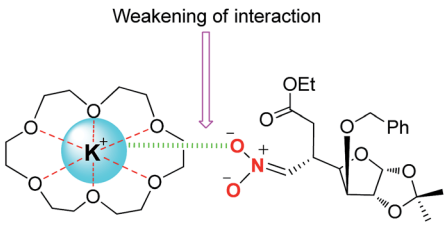
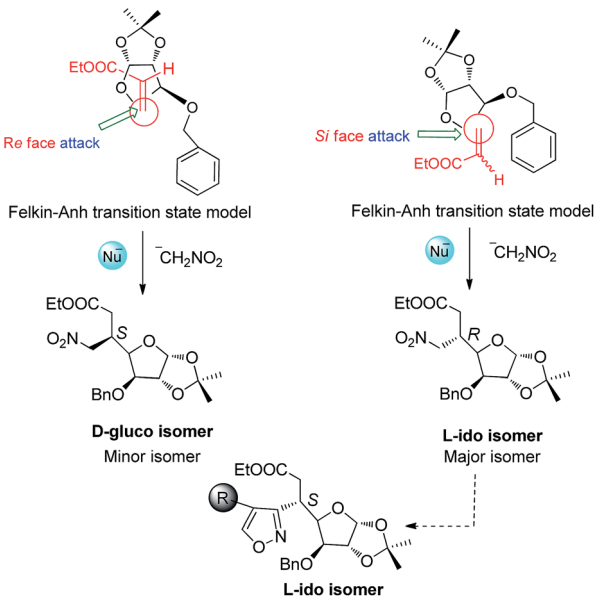


Fig. 2 Showing the probable role of 18-crown-6 ether in the formation of isoxazole-linked glycoconjugates.

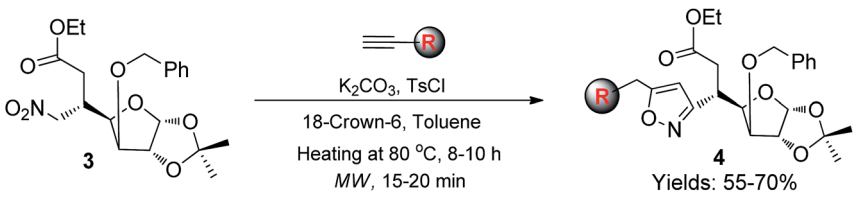
of furanose ring of D-glucose. The ethyl-[3-*O*-ethyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-nitromethyl]-β-L-ido-heptofuranurnate **6** has been prepared from corresponding olefinic ester **5** using the similar protocol as described for compound **3** to afford compound **6** in 87% yield. Utilizing the above established reaction conditions for the formation of isoxazole-linked glycoconjugates, the reaction of compound **6** and different sugar alkynes (**2c**, **2g**, **2i**) afforded **7a–c** in good yields (Scheme 7).



Scheme 6 Formation of L-ido isomer of isoxazole-linked glycoconjugate from *Si* face attack.

After successfully synthesizing various novel isoxazole-linked glycoconjugate **4a–n** and **7a–c**, we turned our attention towards the introduction of isoxazole ring at different positions of sugar derivatives. We know modification of carbohydrates at any specific position has always remained a great challenge for synthetic organic chemists. In this continuation, due to immense biological significance, carbohydrate moiety when integrated with any heterocyclic motifs at specific position alters their physiochemical behavior to a great extent.[33] With this in view, we have utilized our above established reaction conditions for introducing isoxazole ring at different positions of sugar derivatives and prepared a library of novel isoxazole bearing sugar derivatives. Hence, the reaction of nitroethane (1.2 equiv) with various *O*-propargyl ethers of sugar **2b–i** (1.0 equiv) in dry toluene (10.0 mL) with TsCl (1.3 equiv), K_2CO_3 (2.0 equiv) and 18-crown-6 ether (10 mol%) as catalyst at 80 °C

Table 4 Synthesis of library of isoxazole-linked glycoconjugates **4a–n**



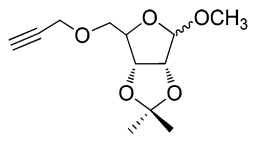
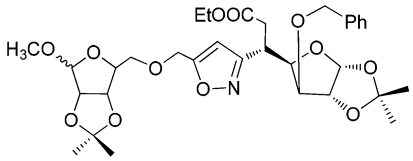
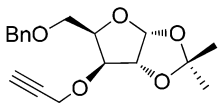
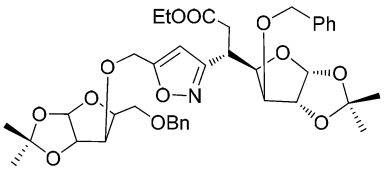
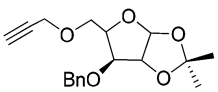
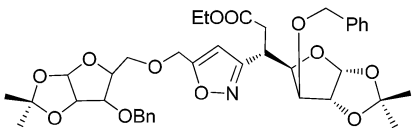
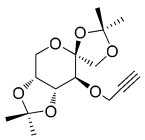
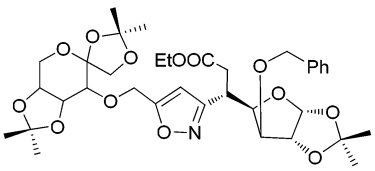
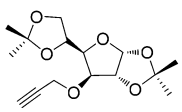
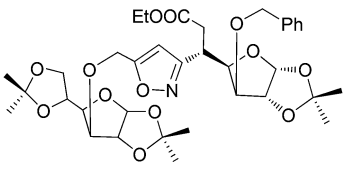
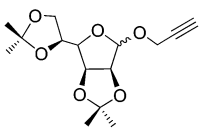
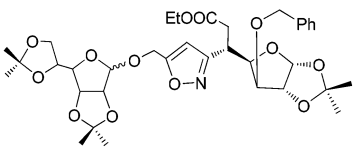
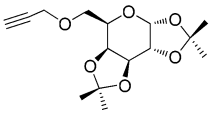
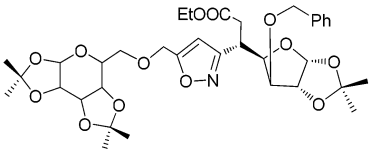
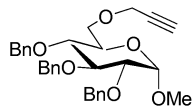
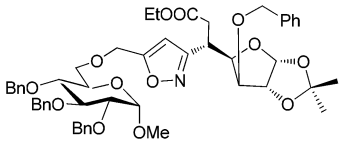
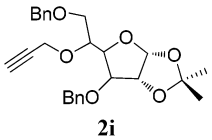
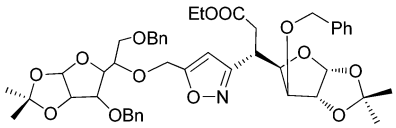
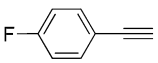
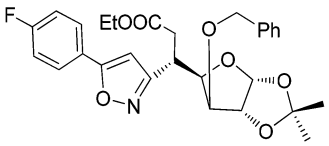
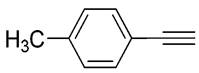
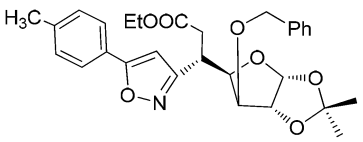
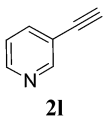
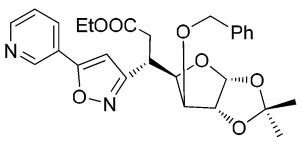
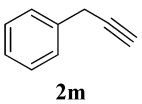
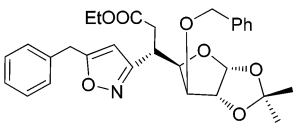
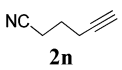
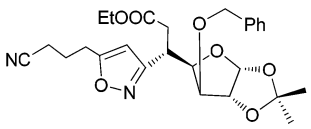
Entry	Alkyne[a]	Cycloadduct	Time[b] t_1 (h)/t_2 (min)	Yield[c] (%) y_1	Yield[d] (%) y_2
1	 **2a**	 **4a**	8/15	69	70
2	 **2b**	 **4b**	8/20	65	68
3	 **2c**	 **4c**	9/15	66	68
4	 **2d**	 **4d**	9/20	65	66
5	 **2e**	 **4e**	8/15	62	63
6	 **2f**	 **4f**	9/20	68	70
7	 **2g**	 **4g**	8/20	66	68

Table 4 (*Contd.*)

8	 **2h**	 **4h**	9/20	66	66
9	 **2i**	 **4i**	8/20	65	67
10	 **2j**	 **4j**	9/20	63	65
11	 **2k**	 **4k**	8/20	56	58
12	 **2l**	 **4l**	8/20	65	66
13	 **2m**	 **4m**	9/20	55	58
14	 **2n**	 **4n**	8/20	68	70

[a] Molar ratios: glycosyl-β-nitromethane ester **3**, terminal alkynes having sugar, alkyl and aryl substituents **2a–n**, TsCl, K_2CO_3 (1 : 1.2 : 1.3 : 2 equivalent) and 18-crown-6 (10 mol%). [b] Reaction time: t_1 = reaction under heating at 80 °C, t_2 = reaction under microwave at 110 °C with a stirring rate 200 rpm. [c] Isolated yield: y_1 = under heating condition. [d] Isolated yield: y_2 = yield under MW condition.

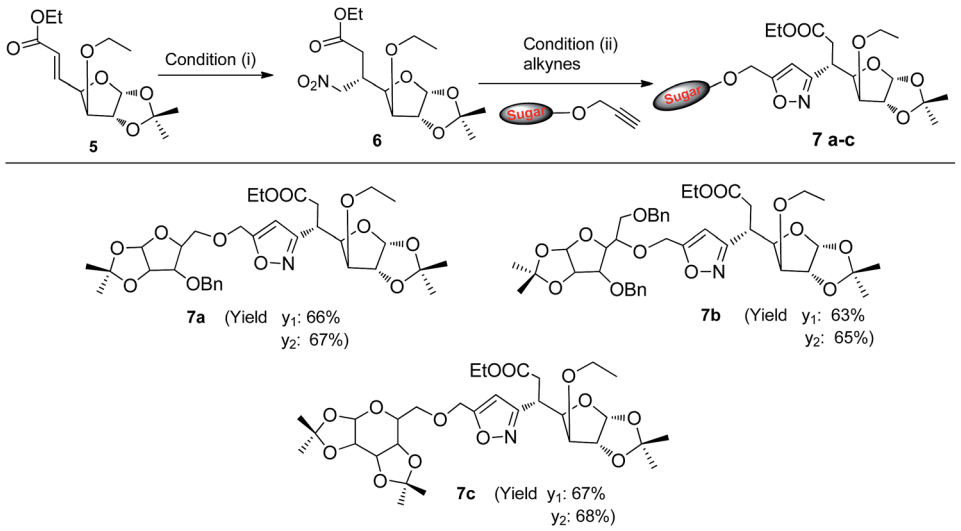
for 8–10 hours as well as under microwave irradiation at 100 W and 110 °C for 15–20 minutes afforded compounds **9a–h** in good yields (Scheme 8).

All the developed compounds of this library have been characterized using extensive spectral studies (IR, ^{1}H, and ^{13}C NMR). Also single-crystal X-ray analysis of compound **9a** clearly showed the presence of isoxazole ring and confirms its unambiguous structure (Fig. 3 and 4; see, ESI for details Fig. D1 and Table D1–D3†).

Similar reaction conditions when applied on 2,5-di-*O*-propargyl-1,4:3,6-dianhydro-D-mannitol (1.0 equiv) and nitroethane (2.2 equiv) in anhydrous toluene (10 mL) with TsCl (2.6 equiv), K_2CO_3 (4.0 equiv) and 18-crown-6 ether (20 mol%) as catalyst at 80 °C for 10 hours as well as under MW irradiation at 100 W and 110 °C for 20 min afforded 1,4:3,6-dianhydro-2,5-bis-*O*-[5′-(methyl)-3′-methyl-isoxazole-5′-yl]-D-mannitol compound **9i** in good yield (Scheme 9).

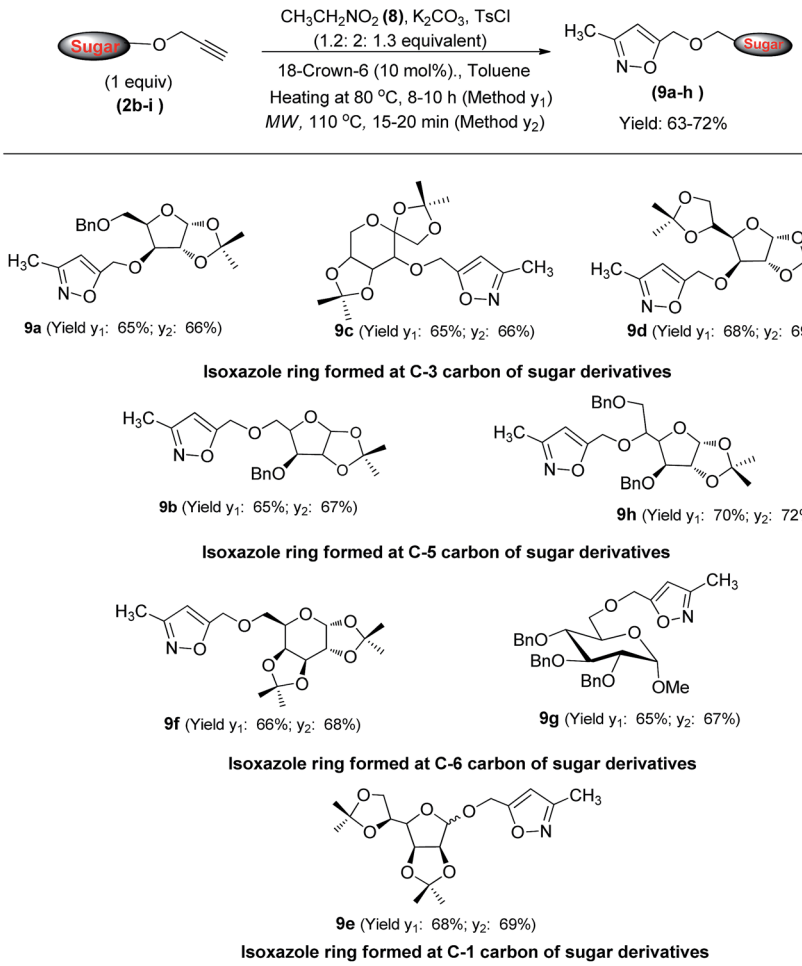
Mechanistic considerations

The proposed mechanism consists of initial formation of glycosyl-β-nitronate **A** which reacts with tosylchloride to give



Reagents and condition: (i) CH_3NO_2, K_2CO_3, Ethanol; (ii) Glycosyl alkyne (**2c, 2g, 2i**), K_2CO_3, TsCl, 18-Crown-6, Toluene, heating at 80 ^{0}C, 8-10 h or *MW*, 15-20 min.
y_1: yield under heating conditions; y_2: yield under microwave conditions

Scheme 7 Synthesis of novel isoxazole-linked glycoconjugates (**7a–c**) from glycosyl olefinic ester.



Scheme 8 Developed library of novel isoxazole-linked glycoconjugates having the isoxazole ring at different positions of sugar derivatives.

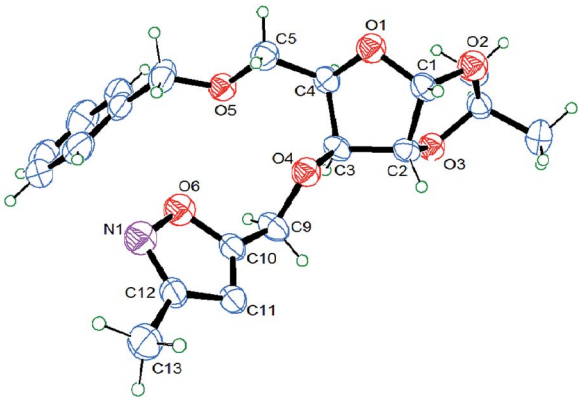


Fig. 3 Molecular structure of **9a**. Thermal ellipsoids of C, N, and O are set at 40% probability.

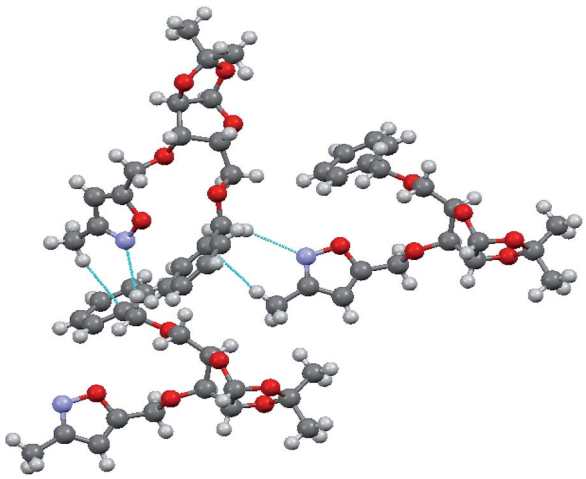
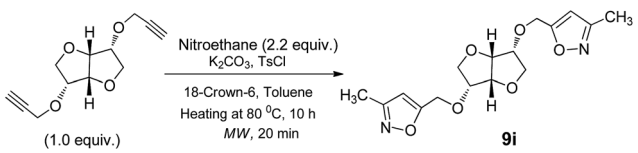


Fig. 4 Showing two types of interaction in **9a**, N…H interaction between N-atom of isoxazole ring and the hydrogen of methylene group attached to phenyl ring; C…H interaction between the hydrogen atom of methyl group and the π-electron density of phenyl ring.



Scheme 9 Synthesis of bis-isoxazole linked D-mannitol derivative.

O-tosylnitronate **B** that can follow two plausible pathways to yield the desired 3,5 disubstituted isoxazoles. Following path **I**, the *O*-tosylnitronate **B** reacts with second mole of K_2CO_3 to furnish glycosyl-β-nitrileoxide ester **C**, which further undergoes [3 + 2] cycloaddition with substituted alkynes to furnish product **4**. However, when the reaction follows path **II**, the *O*-tosylnitronate **B** first reacts with substituted alkynes to yield a new adduct **D**. The adduct **D** then reacts with second mole of K_2CO_3 to give product **4** (Fig. 5).

The reaction follows the proposed mechanism has been further supported by Density Functional Theory (DFT) wherein the geometry of both the intermediates *i.e.* glycosyl-β-nitrile oxide ester **C** and the adduct **D** formed *via* path **I** and **II** respectively, along with glycosyl-β-nitromethane ester **3** and *O*-tosylnitronate **B** were optimized at B3LYP/6-31G (d,p) level of theory in gas phase using Gaussian 09 package.[34] Gauss view 3.09 was used to visualize the optimized molecular geometry, bond length, and bond angles. For each set of calculations, vibrational analysis was done using the same basis set employed in the corresponding geometry optimization. DFT calculations supported the view that glycosyl-β-nitrile oxide ester **C** and adduct **D** formed during the reaction path **I** and **II** are intermediates, not transition states because no negative frequencies are obtained in the DFT based frequency calculation of compound **C** and **D** (Fig. 7 and 8) (see, ESI for details; Fig. D2–D4 and Table D4–D7†).

Secondly, taking a closer look at the transition state involved in the formation of adduct **D** *via* path **II**, we observed that steric factor governs the formation of adduct **D** to a great extent. The transition state of adduct **D** includes alkyne and *O*-toluenesulphonyl group. The *O*-toluenesulphonyl group is very bulky in nature hence it destabilizes the transition state to a considerable extent. As a result the possibility of formation of adduct **D** is minimized, hence disfavouring the reaction to follow path **II**. On the other hand, the transition state involved in the formation of isoxazole-linked glycoconjugates *via* path **I** includes the alkyne and intermediate glycosyl-β-nitrile oxide ester. So no

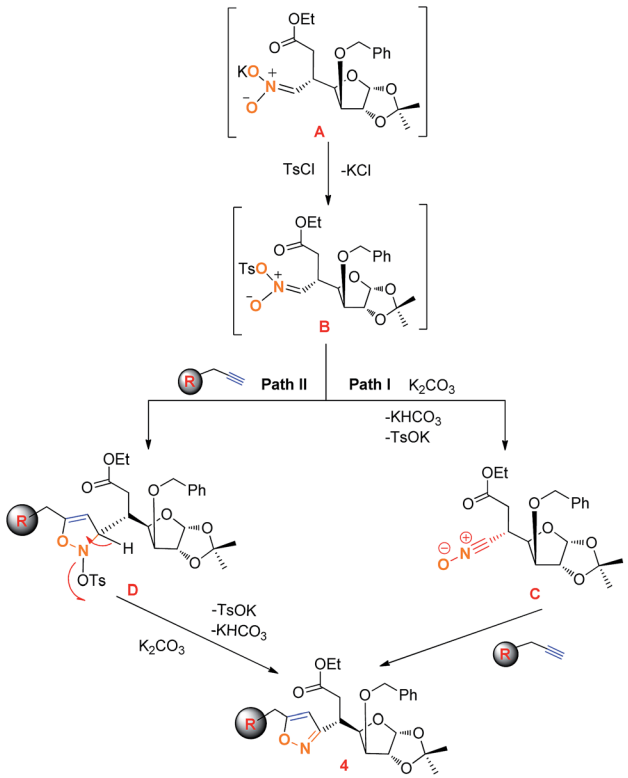


Fig. 5 Proposed mechanism for the formation of isoxazole-linked glycoconjugates.

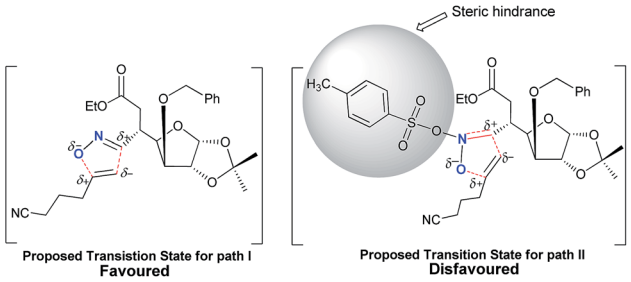


Fig. 6 Proposed transition state for path I and II respectively.

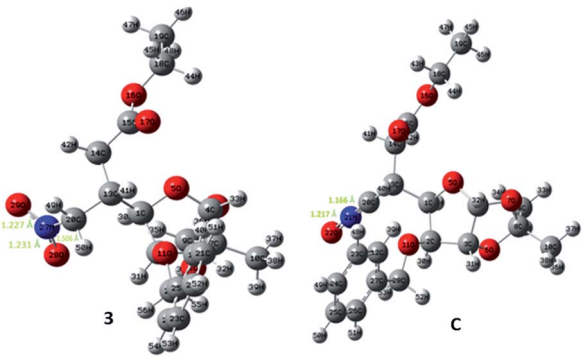


Fig. 7 Optimized geometry of glycosyl-β-nitromethane ester **3** and glycosyl-β-nitrileoxide ester **C** at B3LYP/6-31G (d,p) level of theory in the gas phase. The bond lengths shown are in angstrom (Å); point group: C1; total energy *E*: −1434.87162955 and −1358.44006328 hartree for optimized structures **3** and **C** respectively.

steric hindrance is involved in this transition state, hence it will be more favoured. This extends further support for the reaction to follow path **I** of the proposed mechanism (Fig. 6). Another probable reason, for the reaction to follow path **I**, might be that in this route the *O*-tosylnitronate **B** first reacts with K_2CO_3 and this would be an ionic reaction while in path **II** the *O*-tosylnitronate **B** reacts with an alkyne by a covalent reaction. The probable rate of ionic reaction is faster as compared to covalent reaction. Hence, due to fast reaction rates and stability of the transition states involved in both pathways as discussed earlier, suggests that the reaction would possibly follow path **I** of the proposed mechanism (Fig. 6–8).

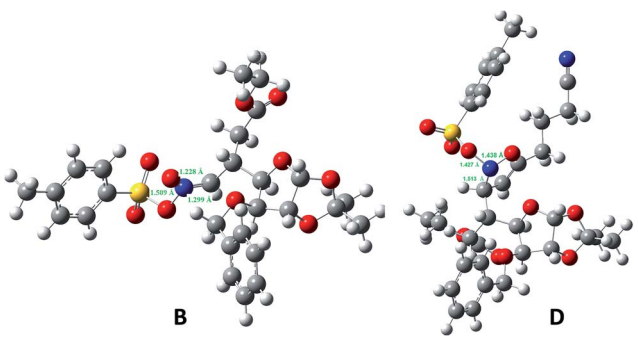


Fig. 8 Optimized geometry of *O*-tosylnitronate B and adduct D at B3LYP/6-31G (d,p) level of theory in the gas phase. The bond lengths shown are in Angstrom (Å); point group: C1; total energy *E*: −2253.79125394 and −2541.37233681 hartree for optimized structure B and D respectively.

Conclusions

A versatile and readily adaptable regioselective one-pot approach has been devised for an easy access to diverse range of novel 3,5-disubstituted isoxazole-linked glycoconjugates *via* [3 + 2] cycloaddition of glycosyl-β-nitrileoxide ester and alkyne. The high regioselectivity, efficiency, less by-product formation, good yield and broad substrate scope are the key features of this methodology. The introduction of isoxazole ring at any specific position of sugar derivative is a salient feature of this reaction strategy. The protocol demonstrates significant compatibility under microwave conditions and thus enhancing its significance from green chemistry perspective. In addition, the wide accessibility to the starting materials is also appealing. Further investigations towards the related reaction of glycosyl-β-nitromethane and their applications are currently underway in our laboratory.

Experimental section

General remarks

All the reactions were carried out in anhydrous solvents under an argon atmosphere in one hour oven dried glassware at 100 °C. Solvents were purified by standard procedures. Yields refer to chromatographically pure material. All reagents and solvents were of pure analytical grade. Thin layer chromatography (TLC) was performed on 60 F_{254} silica gel, pre-coated on aluminium plates and revealed with either a UV lamp (λ_{max} = 254 nm) or a specific colour reagent (*Draggendorff* reagent or iodine vapours) or by spraying with methanolic-H_2SO_4 solution and subsequent charring by heating at 100 °C. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Chemical shifts given in ppm downfield from internal TMS; *J* values in Hz. Mass and the high resolution mass spectra (HRMS) of the developed glycoconjugates were recorded using electro spray ionization mass spectrometry. Infrared spectra recorded as Nujol mulls in KBr plates. Reactions under microwave were carried out in a single-mode microwave reactor from CEM Discover® LabMate, Wattage: 300 W, T-300 °C. Single-crystal X-ray data of compound **9a** was collected on Xcalibur Eos (Oxford) CCD diffractometer using graphite monochromated Mo*Kα* radiation ($\lambda = 0.71073$ Å).

Procedure for the synthesis of orthogonally protected sugars

The protected sugars were prepared from readily available carbohydrates (D-glucose, D-galactose, D-ribose, methyl-D-glucopyranoside and D-xylose) using standard protection methodologies.[25,26]

General procedure for the synthesis of *O*-propargyl ethers of orthogonally protected sugars (2a–i)[27,28]

To a stirred solution of orthogonally protected sugars (1.0 mmol) in dry DMF (10 mL) was added NaH (2.1 mmol)

fractionwise at 0 °C and the reaction was allowed to stir for 10–15 minutes, then propargyl bromide (1.3 mmol) and TBAB (50 mg) were added to the reaction mixture and stirring continued for 10–12 hours at rt. Completion of the reaction was confirmed by TLC (*n*-hexane/ethyl acetate (9 : 1); reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Solvent evaporated under reduced pressure below 55 °C and column chromatography (SiO_2) of crude product using gradient mixtures of *n*-hexane/ethyl acetate afforded the desired sugar alkynes **2a–i**.

3,6-Di-*O*-benzyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose (2i). To a stirred solution of 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (2.0 g, 5.0 mmol) in dry DMF (16 mL) was added with NaH (0.25 g, 10.49 mmol) at 0 °C. The reaction mixture was allowed to stir for 15 minutes, then propargyl bromide (0.63 mL, 6.49 mmol) and TBAB (50 mg) were added and reaction continued for 12 h at room temperature to afford **2i** as yellow liquid (1.83 g, yield 84%). $R_f = 0.51$ (12% ethyl acetate/*n*-hexane); MS: *m*/*z* 461 [M + Na]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 10H), 5.87 (s, 1H), 4.66 (d, $J = 11.7$ Hz, 1H), 4.55 (m, 4H), 4.39 (d, $J = 15.9$ Hz, 1H), 4.26 (m, 1H), 4.22 (d, $J = 6.9$ Hz, 1H), 4.16–4.10 (m, 1H), 4.05-4.00 (m, 1H), 3.90 (1H, $J = 10.8$ Hz, 1H), 3.65 (dd, $J = 5.4$, 10.2 Hz, 1H), 2.33 (s, 1H), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 137.6, 128.3 (2C), 128.2 (2C), 127.7, 127.6 (2C), 127.5, 127.4 (2C), 111.7, 105.0, 81.9, 81.5, 80.1, 78.7, 74.9, 74.1, 73.3, 72.2, 70.8, 57.7, 26.7, 26.3 ppm.

2,5-Di-*O*-propargyl-1,4:3,6-dianhydro-D-mannitol (2o). 1,4:3,6-Dianhydromannitol (5.0 g, 34.2 mmol) dissolved in dry DMF (15 mL) was maintained at 0 °C, subsequently NaH (3.28 g, 136.8 mmol) was added to it and reaction was kept for stirring. After 30 min propargyl bromide (6.7 mL, 75.2 mmol) and TBAB (50 mg) were added to the reaction mixture and stirring continued for overnight. Completion of the reaction was confirmed by TLC monitoring; reaction mixture was extracted with ethyl acetate and dried over Na_2SO_4. Column chromatography (SiO_2) of crude product using hexane/ethyl acetate (9 : 1) as eluant afforded the desired glycosyl alkyne **2o** as white crystalline solid (6.2 g, 82%). MS: *m*/*z* 245 [M + Na]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.61 (s, 2H), 4.36–4.24 (m, 6H), 4.12–4.07 (m, 2H), 3.73 (t, $J = 8.7$ Hz, 2H), 2.4 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.3 (2C), 79.2, 78.7 (3C), 75.1 (2C), 70.9 (2C), 57.6 (2C) ppm.

General procedure for the synthesis of 3,5-disubstituted isoxazole-linked glycoconjugates (4a–i)

To a stirred solution of glycosyl-β-nitromethane ester **3** (1.0 equiv) in dry toluene (10 mL) was added K_2CO_3 (2.0 equiv), *p*-toluenesulphonyl chloride (1.3 equiv), terminal alkynes **2a–n** (1.2 equiv) and 18-crown-6 (10 mol%). The reaction mixture was stirred under refluxing condition for 8–10 h at 80 °C. After completion of reaction (monitored by TLC; *n*-hexane/ethyl acetate, 7 : 3), the reaction mixture was *in vacuo* concentrated and extracted with ethyl acetate, washing with water and saturated brine solution. The obtained organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography (SiO_2) of crude product using gradient mixtures of *n*-hexane/ethyl acetate (7 : 3) as eluant afforded 3,5 disubstituted isoxazole-linked glycoconjugates **4a–n**, **7a–c** and **9a–i** in good yields.

For microwave assisted synthesis, the reaction mixtures were exposed to single-mode microwave reactor CEM Discover® LabMate with a new sealed pressure regulation 10 mL pressurized vial with "snap-on" cap and teflon-coated magnetic stir bar. The standard temperature control system consisted non-contact calibrated infrared sensor which monitors and controls the temperature conditions of the reaction vessel located in the instrument cavity. For each set of reaction with standardized molar ratios of reagents, the reaction temperature was maintained at 110 °C and 200 rpm. After completion of reaction (monitored by TLC; *n*-hexane/ethyl acetate 7 : 3), the reaction mixture was *in vacuo* concentrated and further extraction and purification as similar to conventional heating condition.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(methyl-2″,3″-*O*-isopropylidene-5″-*O*-methyl-β-D-ribofuranoside-5″-yl)-isoxazole (4a). To a stirring solution of glycosyl-β-nitromethane ester **3** (500 mg, 1.22 mmol) in dry toluene (12 mL) was added with *p*-toluenesulphonyl chloride (300 mg, 1.59 mmol), K_2CO_3 (337 mg, 2.44 mmol), methyl-2,3-*O*-isopropylidene-5-*O*-propargyl-β-D-ribofuranoside **2a** (355 mg, 1.47 mmol) and 18-crown-6 (10 mol%). The resulting reaction mixture was refluxed with stirring at 80 °C for 8 h to afford **4a** as pale yellow solid (541 mg, yield 70%). mp 98–100 °C; R_f = 0.51 (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2987, 2934, 1734 (C=O), 1608 (C=N), 1587, 1455, 1374, 1212 (C–O–N), 1164, 1107, 1075, 1023, 961, 869, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.26 (s, 1H), 5.91 (d, $J = 3.6$ Hz, 1H), 4.94 (s, 1H), 4.73 (d, $J = 12$ Hz, 1H), 4.64 (d, $J = 4.2$ Hz, 2H), 4.56 (m, 3H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.34–4.30 (m, 2H), 4.07–4.02 (m, 2H), 3.93 (m, 1H), 3.81–3.75 (m, 1H), 3.59–3.45 (m, 2H), 3.28 (s, 3H), 2.72 (dd, $J = 10.2$, 15.9 Hz, 1H), 2.39 (d, $J = 16.2$ Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.31 (s, 6H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 167.9, 163.8, 136.7, 128.5 (2C), 128.1, 128.0 (2C), 112.3, 111.6, 109.1, 104.7, 104.1, 85.0, 84.8, 81.4, 81.3, 80.9, 80.8, 71.8, 71.5, 64.0, 60.5, 54.7, 34.4, 33.3, 26.6, 26.3, 26.2, 24.9, 14.1 ppm. HRMS calcd for $C_{32}H_{44}NO_{12}$ [M + H]$^+$: 634.2864; found 634.2837.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-l-ido-heptofuranurnate-5′-yl]-5-(5″-*O*-benzyl-1″,2″-*O*-isopropylidene-3″-*O*-methyl-α-D-xylofuranose-3″-yl)-isoxazole (4b). Compound **3** (0.5 g, 1.22 mmol) on treatment with 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose **2b** (0.47 g, 1.47 mmol) in presence of TsCl (0.3 g, 1.59 mmol), K_2CO_3 (0.337 g, 2.44 mmol) and 18-crown-6 (10 mol%) in dry toluene (12 mL) at 80 °C for 8 h and workup as described in general procedure afforded **4b** as yellow liquid (589 mg, yield 68%). $R_f = 0.45$ (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2988, 2935, 1736 (C=O), 1615 (C=N), 1580, 1433, 1369, 1218 (C–O–N), 1169, 1071, 1028, 965, 864, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 10H), 6.24 (s, 1H), 5.91 (d, $J = 4.5$ Hz, 1H), 5.89 (d, $J = 4.2$ Hz, 1H), 4.73 (d, $J = 11.7$ Hz, 1H), 4.64 (d, $J = 3.9$ Hz, 1H), 4.57 (d, $J = 9.6$ Hz, 1H), 4.54–4.43 (m, 4H), 4.38–4.28 (m, 3H), 4.30 (d, $J = 9.9$ Hz,

1H), 4.04 (d, $J = 6.9$ Hz, 1H), 3.99 (d, $J = 2.7$ Hz, 1H), 3.92 (d, $J = 2.4$ Hz, 1H), 3.80–3.76 (m, 2H), 3.71 (d, $J = 6.3$ Hz, 1H), 2.71 (dd, $J = 9.9$, 15.9 Hz, 1H), 2.37 (d, $J = 12.9$ Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.30 (s, 6H), 1.17 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 167.5, 163.9, 137.9, 136.7, 128.5 (2C), 128.3 (2C), 128.1 (2C), 128.0 (2C), 127.8, 127.6, 111.7, 111.6, 105.0, 104.8, 104.1, 82.8, 82.7, 81.3, 80.9, 78.8, 73.5, 71.5, 67.1, 63.2, 60.5, 34.3, 33.3, 26.6 (2C), 26.1 (2C), 14.0 ppm; HRMS calcd for $C_{38}H_{48}NO_{12}$ $[M + H]^+$ 710.3177; found 710.3174.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(3″-*O*-benzyl-1″,2″-*O*-isopropylidine-5″-*O*-methyl-α-D-xylofuranose-4″-yl)-isoxazole (4c). Compound **3** (0.35 g, 0.85 mmol) on treatment with 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-propargyl-α-D-xylofuranose **2c** (312 mg, 1.03 mmol), TsCl (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (12 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4c** as yellow oil (416 mg, yield 70%). $R_f = 0.47$ (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2985, 2937, 1732 (C=O), 1610 (C=N), 1590, 1467, 1376, 1218 (C–O–N), 1166, 1102, 1075, 1015, 966, 856, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.26 (m, 10H), 6.25 (s, 1H), 5.90 (d, $J = 3.9$ Hz, 2H), 5.29 (s, 1H), 4.73–4.66 (m, 5H), 4.61 (d, $J = 11.7$ Hz, 2H), 4.49 (d, $J = 14.7$ Hz, 2H), 4.43-4.31 (m, 1H), 4.03 (d, $J = 6.9$ Hz, 2H), 3.93 (d, $J = 9.3$ Hz, 2H), 3.78 (m, 2H), 2.71(dd, $J = 9.9$, 15.6 Hz, 1H), 2.40 (dd, $J = 3$, 15.9 Hz, 1H) 1.48 (s, 3H), 1.44 (s, 3H), 1.30 (s, 6H), 1.17 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 168.1, 163.8, 137.4, 136.8, 129.7, 129.7, 128.4 (4C), 128.0 (2C), 127.6 (2C), 111.7, 111.6, 105.0, 105.0, 104.0, 82.3, 82.1, 81.4, 81.1, 81.0, 79.0, 72.0, 71.5, 68.6, 64.2, 60.5, 34.5, 33.3, 26.8, 26.7, 26.2, 26.2, 14.0 ppm; HRMS: calcd for $C_{38}H_{47}NO_{12}$ $[M + H]^+$: 710.3177; found 710.3192.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(1″,2″:4″5″-di-*O*-isopropylidene-3″-*O*-methyl-D-fructopyranose-1″-yl)-isoxazole (4d). Compound **3** (0.35 g, 0.85 mmol) on treatment with 1,2:4,5-di-*O*-isopropylidene-3-*O*-propargyl-D-fructopyranose **2d** (305 mg, 1.03 mmol), TsCl (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4d** as yellow liquid (383 mg, yield 65%). $R_f = 0.43$ (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}; 2987, 2946, 1732 (C=O), 1616 (C=N), 1586, 1463, 1378, 1216 (C–O–N), 1164, 1106, 1076, 1021, 965, 850, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.26 (m, 5H), 6.25 (s, 1H), 5.90 (d, $J = 3.6$ Hz, 1H), 4.92 (d, $J = 13.5$ Hz, 1H), 4.78–4.71 (m, 2H), 4.64 (d, $J = 3.9$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.36–4.29 (m, 1H), 4.20–4.14 (m, 2H), 4.07 (d, $J = 8.4$ Hz, 2H), 4.02 (d, $J = 8.4$ Hz, 2H), 3.96-3.84 (m, 4H), 3.50 (d, $J = 7.5$ Hz, 1H), 2.71 (dd, $J = 10.2$, 16.2 Hz, 1H), 2.37 (d, $J = 15.9$ Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 168.2, 163.8, 136.7, 129.2, 128.5 (2C), 128.0 (2C), 112.2, 111.6, 109.2, 104.7, 104.2, 103.9, 81.5, 81.3, 81.1, 80.8, 74.2, 73.7, 71.7, 71.5, 71.4, 63.7, 60.5, 34.4, 33.3, 28.1, 26.9, 26.6, 26.2, 26.1, 25.8, 14.0 ppm; HRMS: calcd for $C_{35}H_{48}NO_{13}$ $[M + H]^+$: 690.3126, found 690.3159.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(1″,2″:5″6″-di-*O*-isopropylidene-3″-*O*-methyl-α-D-glucofuranose-3″-yl)-isoxazole (4e). Compound **3** (250 mg, 0.61 mmol) on treatment with 1,2:5,6 di-*O*-isopropylidene-3-*O*-propargyl-α-D-glucofuranose **2e** (218 mg, 0.73 mmol), TsCl (151 mg, 0.79 mmol), K_2CO_3 (168 mg, 1.22 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **4e** as white liquid (261 mg, yield 62%). $R_f = 0.45$ (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2992, 2940, 1734 (C=O), 1619 (C=N), 1589, 1466, 1374, 1215 (C–O–N), 1169, 1109, 1073, 1019, 961, 853, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.31 (s, 1H), 5.89 (d, $J = 15.3$ Hz, 2H), 4.73 (d, $J = 11.7$ Hz, 2H), 4.68 (d, $J = 5.1$ Hz, 1H), 4.65 (d, $J = 3.3$, 1H), 4.53 (d, $J = 3.3$ Hz, 1H), 4.46 (d, $J = 12$ Hz, 1H), 4.32 (d, $J = 3.9$ Hz, 1H), 4.29 (m, 1H), 4.08 (d, $J = 5.7$ Hz, 1H), 4.03–3.93 (m, 7H), 3.82–3.74 (m, 1H), 2.74 (dd, $J = 10.2$, 16.2 Hz, 1H), 2.37 (d, $J = 13.8$ Hz, 1H), 1.59 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 167.7, 166.7, 136.8, 129.3, 128.5 (2C), 128.0 (2C), 111.9, 111.6, 109.1, 105.1, 104.7, 104.2, 82.6, 81.3, 80.9, 80.8, 79.9, 72.2, 71.6, 71.4, 64.3, 63.6, 56.1, 33.7, 31.9, 26.8, 26.7, 26.4, 26.1, 25.3, 22.6, 14.1 ppm; HRMS: calcd for $C_{35}H_{48}NO_{13}$ $[M + H]^+$: 690.3126; found 690.3137.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(2″,3″:5″,6″-di-*O*-isopropylidene-1″-*O*-methyl-D-mannofuranose-1″-yl)-isoxazole (4f). Compound **3** (0.5 g, 1.22 mmol) on treatment with 2,3:5,6 di-*O*-isopropylidene-1-*O*-propargyl-D-mannofuranose **2f** (0.44 g, 1.47 mmol), TsCl (0.3 g, 1.59 mmol), K_2CO_3 (0.34 g, 2.44 mmol), 18-crown-6 (10 mol%) in dry toluene (12 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4f** as pale yellow oil (589 mg, yield 68%). $R_f = 0.42$ (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2985, 2936, 1732 (C=O), 1610 (C=N), 1432, 1368, 1216 (C–O–N), 1168, 1072, 1025, 968, 865, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.25 (s, 1H), 5.92 (d, $J = 3.3$ Hz, 1H), 5.06 (s, 1H), 4.77 (d, $J = 3.9$ Hz, 1H), 4.72 (d, $J = 11.7$ Hz, 1H), 4.65–4.60 (m, 3H), 4.49 (d, $J = 12.6$ Hz, 1H), 4.44–4.38 (m, 2H), 4.33 (d, $J = 5.1$ Hz, 1H), 4.13–3.93 (m, 6H), 3.80–3.75 (m, 1H), 2.73 (dd, $J = 10.2$, 16.2 Hz, 1H), 2.40 (d, $J = 12.6$ Hz, 1H), 1.45 (s, 9H), 1.38 (s, 3H), 1.31 (s, 6H), 1.18 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 167.3, 163.9, 136.8, 128.5 (2C), 128.1, 127.9 (2C), 112.7, 111.6, 109.2, 105.9, 104.8, 104.3, 84.9, 81.5, 81.2, 81.0, 80.7, 79.3, 72.9, 71.5, 66.8, 60.5, 59.5, 34.4, 33.3, 26.8, 26.7, 26.2, 25.8, 25.2, 24.5, 14.0 ppm; HRMS: calcd for $C_{35}H_{48}NO_{13}$ $[M + H]^+$: 690.3126; found 690.3140.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(1″,2″:3″,4″-di-*O*-isopropylidene-6″-*O*-methyl-α-D-galactopyranose-6″-yl)-isoxazole (4g). Compound **3** (0.35 g, 0.85 mmol) on treatment with 1,2:3,4-di-*O*-isopropylidene-6-*O*-propargyl-α-D-galactopyranose **2g** (0.31 g, 1.03 mmol), (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **4g** as pale yellow liquid (389 mg, yield 66%). $R_f = 0.45$ (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2984, 2933, 1736 (C=O), 1612 (C=N), 1589, 1459, 1369, 1218 (C–O–N), 1166, 1109, 1075, 1025, 966, 872,

732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.26 (m, 5H), 6.26 (s, 1H), 5.91 (d, J = 4.8 Hz, 1H), 5.52 (d, J = 5.1 Hz, 1H), 4.71 (d, J = 11.7 Hz, 1H), 4.67–4.53 (m, 4H), 4.45 (d, J = 12 Hz, 1H), 4.35–4.30 (m, 2H), 4.23 (d, J = 4.8 Hz, 1H), 4.06–4.02 (m, 3H), 3.95 (d, J = 16.2 Hz, 1H), 3.80 (d, J = 9.6 Hz, 1H), 3.76–3.68 (m, 1H), 3.64 (d, J = 9.9 Hz, 1H), 2.72 (dd, J = 9.9, 15.9 Hz, 1H), 2.40 (d, J = 16.2 Hz, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.32 (s, 6H), 1.30 (s, 3H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 168.3, 163.7, 136.8, 128.5 (2C), 128.1, 127.9 (2C), 111.6, 109.2, 108.5, 104.7, 103.8, 96.3, 81.3, 81.1, 71.5, 71.0, 70.6, 70.5, 70.4, 69.8, 66.7, 64.2, 60.5, 34.5, 33.3, 26.7, 26.2, 26.0, 25.9, 24.9, 24.4, 14.0 ppm; HRMS: calcd for $C_{35}H_{48}NO_{13}$ $[M + H]^+$: $C_{35}H_{48}NO_{13}$: 690.3126; found 690.3139.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(methyl-2″,3″,4″tri-*O*-benzyl-6″-*O*-methyl-α-D-glucopyranoside-6″-yl)-isoxazole (4h). Compound **3** (0.25 g, 0.61 mmol) on treatment with methyl-2,3,4-tri-*O*-benzyl-6-*O*-propargyl-α-D-glucopyranoside **2h** (0.39 g, 0.73 mmol), TsCl (151 mg, 0.79 mmol), K_2CO_3 (168 mg, 1.22 mmol) and 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4h** as pale yellow liquid (372 mg, yield 66%). R_f = 0.49 (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2987, 2929, 1733 (C=O), 1615 (C=N), 1594, 1455, 1371, 1216 (C–O–N), 1168, 1112, 1074, 1015, 963, 875, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.24 (m, 20H), 6.24 (s, 1H), 5.89 (d, J = 3.6 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 4.83 (t, J = 10.2 Hz, 1H), 4.74 (d, J = 9 Hz, 1H), 4.69–4.32 (m, 9H), 4.31 (d, J = 9.6 Hz, 1H), 4.01 (d, J = 6.9 Hz, 1H), 3.97–3.94 (m, 2H), 3.91 (d, J = 2.7 Hz, 1H), 3.77 (d, J = 9.6 Hz, 1H), 3.74 (dd, J = 9.6, 16.8 Hz, 1H), 3.62 (d, J = 9.6 Hz, 1H), 3.58–3.55 (m, 2H), 3.51 (d, J = 3.3 Hz, 1H), 3.35 (s, 3H), 2.69 (m, 1H), 2.37 (d, J = 12.9 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H), 1.15 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 168.0, 163.8, 138.7, 138.19, 138.10, 136.8, 128.4 (4C), 128.3 (2C), 128.2 (4C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.6 (2C), 127.4 (2C), 111.5, 104.7, 104.0, 98.0, 81.9, 81.4, 81.3, 81.0, 80.9, 79.7, 75.6, 74.9, 73.3, 71.5, 69.9, 69.4, 64.3, 60.4, 55.1, 34.4, 33.37, 33.31, 26.6, 26.1, 14.0 ppm.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(3″,6″-di-*O*-benzyl-5″-*O*-methyl-1″,2″-*O*-isopropylidene-α-D-glucofuranose-5″-yl)-isoxazole (4i). Compound **3** (0.35 g, 0.85 mmol) on treatment with 3,6-di-*O*-benzyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose **2i** (500 mg, 1.03 mmol), TsCl (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4i** as pale yellow liquid (460 mg, yield 65%); R_f = 0.43 (35% ethyl acetate/*n*-hexane). IR (KBr) ν_{max}: 2994, 2934, 1734 (C=O), 1618 (C=N), 1588, 1459, 1368, 1215 (C–O–N), 1170, 1102, 1073, 1014, 969, 874, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.29 (m, 15H), 6.18 (s, 1H), 5.88 (d, J = 4.2 Hz, 2H), 4.84 (d, J = 12.9 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.66–4.63 (m, 6H), 4.56 (d, J = 11.1 Hz, 1H), 4.45 (d, J = 12.3 Hz, 1H), 4.31 (d, J = 9.6 Hz, 1H), 4.21 (d, J = 6.9 Hz, 1H), 4.16–3.92 (m, 5H), 3.86 (d, J = 10.5 Hz, 1H), 3.80–3.74 (m, 1H), 3.67–3.62 (m, 1H), 2.71 (dd, J = 10.2, 16.2 Hz, 1H), 2.36 (d, J = 15.9 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.30 (s, 6H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 168.6, 163.7, 138.2, 137.5, 136.8, 128.5 (2C), 128.4 (2C), 128.2 (2C), 128.1 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.5, 111.7, 111.5, 105.2, 104.7, 103.6, 81.8, 81.7, 81.4, 81.3, 80.9, 78.8, 73.4, 73.3, 72.1, 71.5, 64.2, 64.1, 60.4, 34.3, 33.3, 26.7 (2C), 26.2 (2C), 14.0 ppm; HRMS: calcd for $C_{46}H_{56}NO_{13}$ $[M + H]^+$: $C_{35}H_{48}NO_{13}$: 830.3752; found 830.3764.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(1″-fluorobenzene-4″-yl)-isoxazole (4j). Compound **3** (0.35 g, 0.85 mmol) on treatment with 1-ethynyl-4-fluorobenzene **2j** (123 mg, 1.03 mmol), (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **4j** as colourless liquid (275 mg, yield 63%). R_f = 0.48 (25% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 3066, 2985, 2926, 2854, 1732 (C=O), 1615 (C=N), 1602, 1511, 1456, 1375, 1235 (C–O–N), 1163, 1075, 1025, 949, 842, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.68 (m, 2H), 7.33 (m, 5H), 7.13–7.07 (m, 2H), 6.48 (s, 1H), 5.94 (d, J = 3.9 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 3.9 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.38 (dd, J = 3, 9.9 Hz, 1H), 4.10–4.04 (m, 2H), 3.95 (d, J = 2.4 Hz, 1H), 3.86–3.79 (m, 1H), 2.78 (dd, J = 10.5, 16.2, 1H), 2.41 (dd, J = 3.6, 15.9 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 168.2, 164.6, 136.8, 128.5 (2C), 128.1, 128.0 (2C), 127.8, 127.7, 124.0, 116.0, 115.7, 111.6, 104.9, 104.7, 100.4, 81.5, 81.3, 80.9, 71.5, 60.5, 34.4, 33.4, 26.6, 26.1, 14.0 ppm.

3-(Ethyl-[3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene]-β-L-ido-heptofuranurnate-5′-yl)-5-(toluene-4″-yl)-isoxazole (4k). Compound **3** (0.35 g, 0.85 mmol) on treatment with 4-ethynyl toluene **2k** (0.13 mL, 1.026 mmol), TsCl (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4k** as pale yellow liquid (242 mg, yield 56%). R_f = 0.54 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 3032, 2984, 2926, 1732 (C=O), 1615 (C=N), 1599, 1455, 1352, 1258 (C–O–N), 1164, 1075, 1025, 820, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 7.8 Hz, 2H), 7.33 (m, 5H), 7.21 (d, J = 8.1 Hz, 2H), 6.48 (s, 1H), 5.95 (d, J = 3.6 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 3.9 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 7.2 Hz, 1H), 4.12–4.03 (m, 2H), 3.95 (d, J = 2.4 Hz, 1H), 3.83 (td, J = 3.9, 10.2 Hz, 1H), 2.78 (dd, J = 10.2, 16.2 Hz, 1H), 2.47–2.40 (m, 1H), 2.37 (s, 3H), 1.46 (s, 3H), 1.31 (s, 3H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 169.3, 164.4, 139.9, 136.8, 129.4 (2C), 128.5 (2C), 128.1, 128.0 (2C), 125.7 (2C), 125.0, 111.6, 104.8, 99.8, 81.5, 81.4, 81.0, 71.5, 60.5, 34.5, 33.5, 26.7, 26.2, 21.4, 14.0 ppm; HRMS: calcd for $C_{29}H_{34}NO_7$ $[M + H]^+$: 508.2335; found 508.2346.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(pyridine-3″-yl)-isoxazole (4l). Compound **3** (0.5 g, 1.22 mmol) on treatment with 3-ethynyl pyridine **2l** (151 mg, 1.47 mmol), TsCl (0.3 g, 1.59 mmol), K_2CO_3 (0.34 g, 2.44 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **4l** as pale yellow solid (403 mg, yield 65%). mp 113–115 °C; R_f = 0.51 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 3127, 2987, 2929, 1735 (C=O), 1620 (C=N), 1581, 1496, 1228 (C–O–N), 1196, 1073, 1041, 812, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.62 (s, 1H), 8.01 (d, J = 7.8 Hz,

1H), 7.33 (m, 6H), 6.64 (s, 1H), 5.95 (d, J = 3.6 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 4.68 (d, J = 3.6 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.37 (d, J = 6.6 Hz, 1H), 4.07 (dd, J = 1.5, 7.2 Hz, 1H), 3.96 (d, J = 3 Hz, 1H), 3.89–3.81 (m, 2H), 2.79 (dd, J = 10.5, 16.2 Hz, 1H), 2.41 (d, J = 15.9 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 166.2, 164.7, 150.5, 146.8, 136.7, 132.8, 132.7, 128.5 (2C), 128.1, 128.0 (2C), 123.5, 111.6, 104.9, 101.8, 81.3, 80.8, 80.7, 71.5, 60.5, 34.3, 33.4, 26.7, 26.2, 14.1 ppm; HRMS: calcd for $C_{27}H_{31}N_2O_7$ $[M + H]^+$: 495.2131; found 495.2139.

3-[Ethyl-(3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(2″-phenylmethan-1″-yl)-isoxazole (4m). Compound **3** (0.35 g, 0.85 mmol) on treatment with 3-phenyl-1-propyne **2m** (0.127 mL, 1.03 mmol), TsCl (212 mg, 1.11 mmol), K_2CO_3 (236 mg, 1.71 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4m** as yellow liquid (238 mg, yield 55%). R_f = 0.51 (25% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 3039, 2983, 2932, 1732 (C=O), 1611 (C=N), 1580, 1458, 1240 (C–O–N), 1163, 1074, 1030, 860, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.21 (m, 10H), 5.91 (s, 1H), 5.90 (d, J = 3.6 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 3.6 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.33 (d, J = 6.6 Hz, 1H), 4.34–4.31 (m, 1H), 4.05–4.00 (m, 3H), 3.90 (d, J = 2.7 Hz, 1H), 3.77–3.70 (m, 1H), 2.69 (dd, J = 9.9, 16.2 Hz, 1H), 2.38 (dd, J = 3.6, 15.9 Hz, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 165.5, 163.8, 136.8, 136.0, 129.8, 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.1, 127.9, 126.9, 111.6, 104.7, 102.8, 81.5, 81.3, 81.1, 71.5, 60.4, 34.5, 33.7, 33.2, 26.6, 26.2, 14.0 ppm; HRMS: calcd for $C_{29}H_{34}NO_7$ $[M + H]^+$: 508.2335; found 508.2341.

3-(Ethyl-[3′-*O*-benzyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene]-β-L-ido-heptofuranurnate-5′-yl)-5-(3″cyanopropan-1″-yl)-isoxazole (4n). Compound **3** (0.5 g, 1.22 mmol) on treatment with 5-cyano-1-pentyne **2n** (0.153 mL, 1.47 mmol), TsCl (300 mg, 1.59 mmol), K_2CO_3 (337 mg, 2.44 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **4n** as pale yellow liquid (589 mg, yield 68%). R_f = 0.47 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2927, 2247, 1732 (C=O), 1604 (C=N), 1455, 1375, 1260 (C–O–N), 1165, 1075, 1024, 857, 806, 700, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 6.06 (s, 1H), 5.92 (d, J = 3.3 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 3.9 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.32 (d, J = 6.9 Hz, 1H), 4.06 (d, J = 7.2 Hz, 2H), 3.93 (m, 1H), 3.79–3.72 (m, 1H), 2.88–2.83 (m, 2H), 2.70 (dd, J = 7.2, 16.2 Hz, 1H), 2.40–2.35 (m, 3H), 2.03 (d, J = 7.2 Hz, 1H), 1.99 (d, J = 6.9 Hz, 1H), 1.46 (s, 3H), 1.31 (s, 3H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 169.7, 164.0, 136.7, 128.4 (2C), 128.1, 127.9 (2C), 118.7, 111.6, 104.7, 102.7, 81.4, 81.2, 80.9, 71.5, 60.5, 34.5, 33.3, 26.6, 26.1, 25.4, 23.2, 16.4, 14.0 ppm; HRMS: calcd for $C_{26}H_{33}N_2O_7$ $[M + H]^+$: 485.2288; found 485.2296.

Ethyl-[3-*O*-ethyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-gluco]-heptfuran-5-en-uronate (5). D-Glucose after processing through a number of high-yielding steps such as isopropylidene protection, 3-*O*-ethyl protection, selective 5,6-isopropylidene deprotection, $NaIO_4$ oxidation, and finally the HEW modification[23] afforded the glycosyl olefinic ester **5** as colourless liquid (Yield 80%); R_f = 0.45 (10% ethyl acetate/*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (dd, J = 5.1, 15.9 Hz, 1H), 6.16 (d, J = 15.6 Hz, 1H), 5.96 (d, J = 3.3 Hz, 1H), 4.78 (s, 1H), 4.59 (d, J = 3.3 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.88 (d, J = 2.7 Hz, 1H), 3.66–3.56 (m, 1H), 3.52–3.44 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 141.2, 122.9, 111.5, 104.8, 83.6, 82.8, 79.2, 66.0, 60.1, 26.5, 25.9, 14.8, 13.9 ppm.

Ethyl-[3-*O*-ethyl-5,6-dideoxy-1,2-*O*-isopropylidene-5-nitro-methyl]-β-L-ido-heptofuranurnate (6). A stirred solution of compound **5** (2.0 g, 6.99 mmol) and nitromethane (0.823 mL, 0.015 mol) in presence of K_2CO_3 (1.93 mg, 0.013 mol) at refluxing temperature for 6 h in anhydrous ethanol (20 mL) afforded **6** which was purified by flash column chromatography using gradient mixtures of *n*-hexane and EtOAc (8 : 2). Colourless liquid, 2.11 g, yield 87%; R_f = 0.51 (15% ethyl acetate/*n*-hexane), ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (s, 1H), 4.79 (d, J = 13.2 Hz, 1H), 4.61–4.51 (m, 2H), 4.15–4.10 (m, 3H), 3.75–3.67 (m, 2H), 3.41 (s, 1H), 3.01 (m, 1H), 2.45 (d, J = 4.5 Hz, 2H), 1.42 (s, 3H), 1.27 (s, 3H), 1.25–1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 111.7, 104.6, 82.0, 81.7, 78.9, 75.5, 65.5, 60.8, 33.4, 33.0, 26.6, 26.2, 15.0, 14.0 ppm.

3-[Ethyl-(3′-*O*-ethyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(3″-*O*-benzyl-1″,2″-*O*-isopropylidene-4″-*O*-methyl-α-D-xylofuranose-4″-yl)-isoxazole (7a). Compound **6** (450 mg, 1.29 mmol) on treatment with 3-*O*-benzyl-1,2-*O*-isopropylidene-4-*O*-propargyl-α-D-xylofuranose **2c** (494 mg, 1.55 mmol), TsCl (320 mg, 1.68 mmol), K_2CO_3 (355 mg, 2.59 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **7a** as pale yellow liquid (562 mg, yield 67%). R_f = 0.32 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2986, 2937, 1732 (C=O), 1610 (C=N), 1590, 1467, 1376, 1217 (C–O–N), 1166, 1101, 1075, 1015, 964, 856, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.30 (m, 5H), 6.22 (s, 1H), 5.92 (d, J = 3.3 Hz, 1H), 5.89 (d, J = 3.9 Hz, 1H), 5.87–4.47 (m, 6H), 4.25–4.29 (m, 2H), 4.18–3.95 (m, 3H), 3.86–3.61 (m, 5H), 3.51–3.40 (m, 1H), 2.83–2.78 (m, 1H), 2.70 (d, J = 3.9 Hz, 1H), 1.45 (s, 6H), 1.31 (s, 6H), 1.21–1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 168.1, 163.9, 137.3, 128.4 (2C), 127.9, 127.6 (2C), 111.7, 111.5, 105.0, 104.8, 103.8, 82.2, 82.1, 81.6, 81.3, 81.1, 79.0, 72.0, 68.5, 65.5, 64.2, 60.5, 34.6, 33.5, 26.7 (2C), 26.2 (2C), 15.0, 14.0 ppm.

3-[Ethyl-(3′-*O*-ethyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(3″,6″-di-*O*-benzyl-5″-*O*-methyl-1″,2″-*O*-isopropylidene-α-D-glucofuranose-5″-yl)-isoxazole (7b). Compound **6** (450 mg, 1.29 mmol) on treatment with 3,6-di-*O*-benzyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose **2i** (680 mg, 1.55 mmol), TsCl (320 mg, 1.68 mmol), K_2CO_3 (355 mg, 2.59 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 9 h and workup as described in general procedure afforded **7b** as yellow liquid (646 mg, yield 65%). R_f = 0.47 (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2994, 2934, 1734 (C=O), 1618 (C=N), 1588, 1459, 1366, 1214 (C–O–N), 1170, 1102, 1075, 1014, 968, 874, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.30 (m, 10H), 6.20 (s, 1H), 5.89 (s, 2H), 4.85 (d, J = 12.9 Hz, 1H), 4.63–4.45 (m, 6H), 4.35 (d, J = 9.3 Hz, 1H), 4.19–4.05 (m, 6H), 3.89–3.43 (m, 6H), 2.81 (d, J = 9.3 Hz, 1H), 2.65 (dd, J = 3.3,

15.9 Hz, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.30 (s, 6H), 1.20–1.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 168.6, 163.8, 137.5 (2C), 129.7, 129.5, 128.4 (2C), 128.3 (2C), 127.7 (2C), 127.5 (2C), 111.7 (2C), 105.1, 104.8, 103.6, 84.2, 82.0, 81.8, 81.6, 81.2, 78.8, 73.3, 72.2, 71.6, 71.5, 65.5, 63.7, 60.5, 37.3, 33.5, 26.7 (2C), 26.2 (2C), 15.1, 14.0 ppm; HRMS: calcd for $C_{41}H_{54}NO_{13}$ $[M + H]^+$: 768.3595; found 768.3588.

3-[Ethyl-(3′-*O*-ethyl-5′,6′-dideoxy-1′,2′-*O*-isopropylidene)-β-L-ido-heptofuranurnate-5′-yl]-5-(1″,2″:3″,4″-di-*O*-isopropylidene-6″-*O*-methyl-α-D-galactopyranose-6″-yl) isoxazole (7c). Compound **6** (300 mg, 0.86 mmol) on treatment with 1,2:3,4-di-*O*-isopropylidene-6-*O*-propargyl-α-D-galactopyranose **2g** (309 mg, 1.03 mmol), TsCl (214 mg, 1.12 mmol), K_2CO_3 (238 mg, 1.72 mmol), and 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **7c** as yellow liquid (368 mg, yield 68%). R_f = 0.30 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2984, 2933, 1736 (C=O), 1612 (C=N), 1589, 1457, 1369, 1218 (C–O–N), 1166, 1109, 1075, 1024, 966, 873, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.28 (s, 1H), 5.90 (s, 1H), 5.53 (d, J = 4.8 Hz, 1H), 4.68–4.59 (m, 3H), 4.55 (d, J = 3.3 Hz, 1H), 4.38 (d, J = 9 Hz, 1H), 4.31 (m, 1H), 4.24 (d, J = 7.8 Hz, 1H), 4.09 (d, J = 6.9 Hz, 2H), 4.05–3.98 (m, 2H), 3.82–3.62 (m, 4H), 3.45 (d, J = 6.9 Hz, 1H), 2.90–2.81 (m, 1H), 2.69 (d, J = 15.9 Hz, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.33 (s, 6H), 1.30–1.17 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 168.4, 163.8, 111.5, 109.2, 108.5, 104.8, 103.8, 96.2, 82.1, 81.6, 81.1, 71.0, 70.6, 70.4, 69.8, 66.8, 65.5, 64.2, 60.5, 34.6, 33.6, 26.7, 26.2, 26.0, 25.9, 24.8, 24.3, 15.1, 14.0 ppm.

3-Methyl-5-(5′-*O*-benzyl-1′,2′-*O*-isopropylidene-3′-*O*-methyl-α-D-xylofuranose-3′-yl)-isoxazole (9a). Nitroethane **8** (0.07 mL, 1.32 mmol) on treatment with 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose **2b** (350 mg, 1.10 mmol), TsCl (272 mg, 1.43 mmol), K_2CO_3 (304 mg, 2.20 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **9a** as white crystalline solid (268 mg, yield 65%). R_f = 0.58 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2924, 2854, 1785 (C=O), 1613 (C=N), 1454, 1374, 1215 (C–O–N), 1165, 1076, 1018, 890, 858, 745, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H), 6.04 (s, 1H), 5.90 (d, J = 3.3 Hz, 1H), 4.66 (d, J = 13.8 Hz, 2H), 4.60 (d, J = 6.9 Hz, 1H), 4.56 (d, J = 2.1 HZ, 1H), 4.54 (d, J = 5.1, 1H), 4.49–4.39 (m, 1H), 4.00 (d, J = 2.4 Hz, 1H), 3.77–3.72 (m, 2H), 2.24 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 159.6, 137.7, 128.3 (2C), 127.7, 127.6 (2C), 111.7, 104.8, 103.7, 82.2 (2C), 78.6, 73.4, 66.8, 62.8, 26.6, 26.1, 11.2 ppm; HRMS: calcd for $C_{20}H_{26}NO_6$: $[M + H]^+$: 376.1760; found 376.1769.

3-Methyl-5-(3′-*O*-benzyl-1′,2′-*O*-isopropylidene-5′-*O*-methyl-α-D-xylofuranose-5′-yl)-isoxazole (9b). Nitroethane **8** (0.19 mL, 2.70 mmol) on treatment with 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-propargyl-α-D-xylofuranose **2c** (500 mg, 1.57 mmol), TsCl (150 mg, 2.04 mmol), K_2CO_3 (434 mg, 3.14 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **9b** as yellow liquid (383 mg, yield 65%). R_f = 0.45 (25% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2938, 2864, 1770 (C=O), 1613 (C=N), 1585, 1448, 1370, 1219 (C–O–N), 1170, 1108, 1074, 1020, 963, 876, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 6.07 (s, 1H), 5.92 (s, 1H), 4.68–4.46 (m, 5H), 4.36 (m, 1H), 3.95 (m, 1H), 3.77 (m, 2H), 2.26 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 159.5, 137.2, 128.3 (2C), 127.8, 127.5 (2C), 111.6, 105.0, 103.5, 82.9, 81.6, 79.0, 71.8, 68.4, 64.0, 26.6, 26.1, 11.2 ppm.

3-Methyl-5-(1′,2′:4′,5′-di-*O*-isopropylidene-3′-*O*-methyl-D-fructo-pyranose-3″-yl) isoxazole (9c). Nitroethane **8** (0.10 mL, 1.40 mmol) on treatment with 1,2:4,5-di-*O*-isopropylidene-3-*O*-propargyl-D-fructopyranose **2d** (350 mg, 1.17 mmol), TsCl (291 mg, 1.52 mmol), K_2CO_3 (324 mg, 2.34 mmol), and 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **9c** as yellow liquid (271 mg, yield 65%). R_f = 0.49 (25% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2939, 2855, 1753 (C=O), 1614 (C=N), 1607, 1460, 1358, 1263 (C–O–N), 1160 1132, 1075, 1020, 954, 873, 869, 632 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (s, 1H), 5.30 (s, 1H), 4.95 (d, J = 13.5 Hz, 1H), 4.78 (d, J = 13.5 Hz, 1H), 4.37–4.33 (m, 1H), 4.22–4.15 (m, 1H), 4.11–3.98 (m, 2H), 3.89 (d, J = 8.7 Hz, 1H), 3.52 (d, J = 7.5 Hz, 1H), 2.29 (s, 3H), 1.54 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 159.5, 112.2, 109.1, 103.9, 103.6, 77.4 (2C), 73.7, 71.6, 63.6, 60.0, 28.0, 26.7, 26.1, 25.8, 11.3 ppm.

3-Methyl-5-(1′,2′:5′,6′-di-*O*-isopropylidene-3′-*O*-methyl-α-D-glucofuranose-3′-yl)-isoxazole (9d). Nitroethane **8** (0.14 mL, 2.01 mmol) on treatment with 1,2:5,6-di-*O*-isopropylidene-3-*O*-propargyl-α-D-glucofuranose **2e** (500 mg, 1.67 mmol), TsCl (415 mg, 2.18 mmol), K_2CO_3 (463 mg, 3.35 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 10 h and workup as described in general procedure afforded **9d** as yellow liquid (405 mg, yield 68%). R_f = 0.59 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2929, 2858, 1756 (C=O), 1611 (C=N), 1604, 1453, 1358, 1265 (C–O–N), 1158, 1132, 1073, 1025, 958, 872, 638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.17 (s, 1H), 5.88 (d, J = 3.6 Hz, 1H), 4.72 (m, 2H), 4.43 (d, J = 3.6 HZ, 1H), 4.29 (dd, J = 5.7, 13.8 Hz, 1H), 4.13–4.08 (m, 2H), 4.03–3.96 (m, 2H), 2.30 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 159.6, 111.8, 109.0, 105.2, 103.6, 82.7, 82.2, 81.0, 72.1, 67.3, 63.3, 26.8, 26.7, 26.0, 25.3, 11.2 ppm.

3-Methyl-5-(2′,3′:5′,6′-di-*O*-isopropylidene-1′-*O*-methyl-D-mannofuranose-1′-yl) isoxazole (9e). Nitroethane **8** (0.14 mL, 2.01 mmol) on treatment with 2,3:5,6-di-*O*-isopropylidene-1-*O*-propargyl-D-mannofuranose **2f** (500 mg, 1.67 mmol), TsCl (415 mg, 2.18 mmol), K_2CO_3 (168 mg, 1.221 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **9e** as yellow liquid (393 mg, yield 66%). R_f = 0.56 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2932, 2860, 1754 (C=O), 1612 (C=N), 1606, 1455, 1356, 1266 (C–O–N), 1158 1133, 1072, 1024, 956, 875, 636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.07 (s, 1H), 4.80–4.77 (m, 1H), 4.65 (d, J = 7.5 Hz, 1H), 4.60 (d, J = 9.9 Hz, 1H), 4.54 (m, 1H), 4.41–4.37 (m, 1H), 4.12–4.07 (m, 1H), 4.00 (d, J = 4.5 Hz, 1H), 3.96 (dd, J = 3.9, 7.5 Hz, 1H), 2.29 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 159.7, 112.7, 109.1, 105.8, 103.9, 84.8, 80.6, 79.3, 72.9, 66.6, 59.4, 26.8, 25.7, 25.1, 24.4, 11.1 ppm.

3-Methyl-5-(1′,2′:3′,4′-di-*O*-isopropylidene-6′-*O*-methyl-α-D-galactopyranose-6′-yl) isoxazole (9f). Nitroethane **8** (0.105 mL, 1.40 mmol) on treatment with 1,2:3,4-di-*O*-isopropylidene-6-*O*-

propargyl-α-D-galactopyranose **2g** (350 mg, 1.17 mmol), TsCl (291 mg, 1.52 mmol), K_2CO_3 (324 mg, 2.34 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 8 h and workup as described in general procedure afforded **9f** as yellow liquid (271 mg, yield 65%). $R_f = 0.51$ (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2954, 2864, 1753 (C=O), 1628 (C=N), 1518, 1462, 1357, 1262 (C–O–N), 1158, 1135, 1072, 1025, 953, 876, 880, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.04 (s, 1H), 5.47 (d, J = 4.8 Hz, 1H), 4.56 (d, J = 9.9 Hz, 1H), 4.51 (d, J = 7.2 Hz, 2H), 4.24 (d, J = 3.0 Hz, 1H), 4.17 (d, J = 7.5 Hz, 1H), 3.90 (d, J = 5.7 Hz, 1H), 3.69–3.56 (m, 2H), 2.22 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.26 (s, 6H) ppm.

3-Methyl-5-(1′-*O*-methyl-2′,3′,4′-tri-*O*-benzyl-6′-*O*-methyl-α-D-glucopyranoside-6′-yl) isoxazole (9g). Nitroethane **8** (0.035 mL, 0.478 mmol) on treatment with methyl-2,3,4-tri-*O*-benzyl-6-*O*-propargyl-α-D-glucopyranoside **2h** (200 mg, 0.478 mmol), TsCl (98 mg, 0.517 mmol), K_2CO_3 (110 mg, 0.79 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 10 h and workup as described in general procedure afforded **9g** as yellow liquid (156 mg, yield 70%). R_f = 0.53 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2925, 1730 (C=O), 1606 (C=N), 1496, 1453, 1360, 1277 (C–O–N), 1136, 1109, 1096, 1070, 913, 806, 742, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.13 (m, 15H), 5.95 (s, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.80–4.69 (m, 3H), 4.59–4.38 (m, 4H), 3.97–3.84 (m, 2H), 3.66 (d, J = 14.7 Hz, 1H), 3.60–3.43 (m, 4H), 3.29 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 159.6, 138.6, 138.1 (2C), 128.4 (4C), 128.3 (2C), 128.0 (2C), 127.9 (2C), 127.7 (2C), 127.6 (2C), 127.5, 103.7, 98.1, 81.9, 79.7, 76.5, 75.7, 74.9, 73.3, 69.8, 69.2, 64.0, 55.1, 11.2 ppm.

3-Methyl-5-(3′,6′-di-*O*-benzyl-5′-*O*-methyl-1′,2′-*O*-isopropylidene-α-D-glucofuranose-5′-yl) isoxazole (9h). Nitroethane **8** (0.05 mL, 0.821 mmol) on treatment with 3,6-di-*O*-benzyl-5-*O*-propargyl-1,2-*O*-isopropylidene-α-D-glucofuranose **2i** (300 mg, 0.68 mmol), TsCl (169 mg, 0.89 mmol), K_2CO_3 (189 mg, 1.36 mmol), 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 10 h and workup as described in general procedure afforded **9h** as yellow liquid (220 mg, yield 63%). R_f = 0.52 (30% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2988, 2932, 2862, 1728 (C=O), 1613 (C=N), 1497, 1454, 1374, 1216 (C–O–N), 1165, 1138, 1075, 1026, 890, 739, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.27 (m, 10H), 5.93 (s, 1H), 5.88 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 12.9 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.63–4.58 (m, 1H), 4.54–4.45 (m, 4H), 4.21 (dd, J = 3.0, 9.0 Hz, 1H), 4.09 (d, J = 2.7 Hz, 1H), 4.06–4.01 (m, 1H), 3.89 (d, J = 10.5 Hz, 1H), 3.66 (dd, J = 6.3, 10.5 Hz, 1H), 2.19 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 159.4, 138.1, 137.3, 128.3 (2C), 128.1 (2C), 127.7, 127.4, 127.4, 127.2 (3C), 111.6, 105.0, 103.3, 81.57, 81.50, 78.6, 75.9, 73.3, 71.8, 71.4, 63.5, 26.6, 26.1, 11.1 ppm.

1,4:3,6-Dianhydro-2,5-bis-*O*-[5′-(methyl)-3′-methyl-isoxazole-5′-yl]-D-mannitol (9i). Nitroethane **8** (0.40 mL, 5.40 mmol) on treatment with 2,5-di-*O*-propargyl-1,4:3,6-dianhydro-D-mannitol **2o** (500 mg, 2.25 mmol), TsCl (1.11 g, 5.84 mmol), K_2CO_3 (1.24 g, 9.0 mmol), and 18-crown-6 (10 mol%) in dry toluene (10 mL) at 80 °C for 10 h and workup as described in general procedure afforded **9i** as yellow liquid (469 mg, yield 62%). R_f = 0.51 (35% ethyl acetate/*n*-hexane); IR (KBr) ν_{max}: 2990, 2929, 1756 (C=O), 1611 (C=N), 1592, 1455, 1356, 1212 (C–O–N), 1170, 1112, 1074, 1032, 964, 865, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.14 (s, 2H), 4.76 (d, J = 13.8 Hz, 1H), 4.65 (s, 1H), 4.55 (d, J = 2.4 Hz, 2H), 4.44–4.27 (m, 2H), 4.23 (d, J = 2.4 Hz, 1H), 4.12 (d, J = 4.5 Hz, 1H), 4.08 (d, J = 7.2 HZ, 1H), 4.02–3.97 (m, 1H), 3.76–3.65 (m, 2H), 2.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (2C), 159.7 (2C), 103.9, 103.8, 80.2, 79.7, 79.0, 78.4, 75.1, 71.0, 62.9, 57.5, 11.2, 11.2 ppm.

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