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via an Aqueous / Ionic-Liquid Route and "Click" Chemistry**

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Vinyl Sulfone Modified- Azidofuranoside Building-Blocks: 1,4-/1,5-Disubstituted-1,2,3-Triazole Linked Trisaccharides via an Aqueous / Ionic-Liquid Route and “Click” Chemistry†

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1,5-Disubstituted 1,2,3-triazole (1,5-DT) linked disaccharides have been synthesized from stable building blocks having both vinyl sulfone and azido groups using aqueous ionic-liquid media. These building blocks containing secondary azido group, do not undergo self-coupling but react with the externally delivered primary azidosugars. The disaccharides are coupled with appropriate building blocks for the preparation of first ever 1,5-DT linked- and 1,4-/1,5-DT-linked trisaccharides using aqueous ionic-liquid and water-butanol based “click” chemistry respectively.

The discovery of the efficient and regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles (1,4-DTs) by Cu(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction, triggered the use of this planar and robust heterocyclic moiety as a “solid keystone”- like unit^{1a} for the conjugation of biomolecules.^{1b,c} Since carbohydrates, an important class of densely functionalized biomolecules is easily and selectively functionalized with azide or alkyne group, coupling of a monofunctionalized carbohydrate with complementary monofunctionalized counterpart generated a wide range of 1,4-DT-modified monosaccharides within a very short span of time.^{1,2} However, very soon the prevailing demand for new molecules as glycomimetics required in the area of glycobiology and glycomics led to the synthesis of polycarbohydrates, where multiple 1,4-DTs were used³ for linking several carbohydrates either in a linear fashion like **1**,^{3a} **2**^{3f} or **3**^{3g} or in a branched architecture as in **4**^{3k} (Figure 1).¹⁻³ The research thereafter proliferated in designing diverse clusters or architectures mimicking glycoclusters, glycodendrimers etc^{2b} having several 1,4-DT units as linkers of carbohydrates or carbohydrates modified with associated linkers.¹⁻³

However, the efficiency of CuAAC coupling and the popular trend of using 1,4-DT as a linker for carbohydrates overshadowed the potential of the corresponding 1,5-DT-linked saccharides.^{4,5}

Although several strategies have been reported for the synthesis of 1,5-DTs, only limited effort has been made to apply those methods for the preparation of 1,5-DT-modified carbohydrates.^{4,5} Since 1,5-DTs in general are known to elicit useful responses in biological systems,^{4,6} it may be argued that limitations of the available synthetic methods including that of the ruthenium based strategy^{4c,5c} considerably slowed down any attempt to synthesize the 1,5-DT-linked polysaccharides.

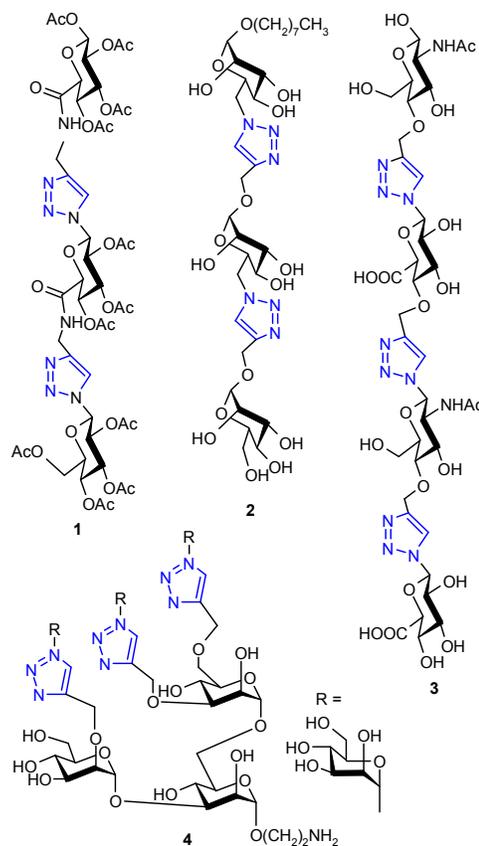


Figure 1: Reported 1,4-DT linked trisaccharides and a tetrasaccharide

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† Electronic Supplementary Information (ESI) available: Experimental section; ¹H/¹³C/DEPT spectrum, HRMS data, rotation value of the compounds. See DOI: 10.1039/b000000x/

We had developed a metal-free methodology for the synthesis of 1,5-DTs based on the 3+2 cycloaddition of organic azides with vinyl sulfones.^{5,6} Using this strategy we synthesized several

disaccharides and some of these synthetic disaccharides were used for the generation of antimicrobial silver nano particles^{5b} via metal chelation. This interesting observation prompted us to synthesize more complex triazole-linked polysaccharides having at least one 1,5-DT unit. On the other hand, as far as our knowledge goes into literature,⁴⁻⁶ there were no report on the synthesis of 1,5-DT linked trisaccharides or mixed trisaccharides made of both 1,4- and 1,5-DT-linkers.

To achieve such a synthesis it was necessary to design appropriate building blocks containing both the vinyl sulfone group and azido group attached to two different positions of the same carbohydrate molecule and our initial target was to design building blocks **5-7** (Figure 2) available easily from the sugar epoxides. We intended to couple these building blocks with the azidofuranosides **8^{5e}**, **9^{5e}** and a vinyl sulfone-modified carbohydrate **10^{5a}** (Figure 3). A propargylated pyranoside **11⁷** (Figure 3) was selected for introducing the 1,4-DT-linkage in the polysaccharides.

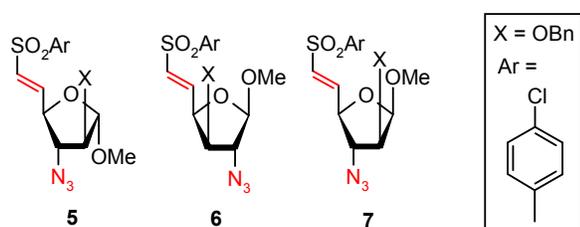


Figure 2: Building blocks vinyl sulfone modified-azidofuranosides.

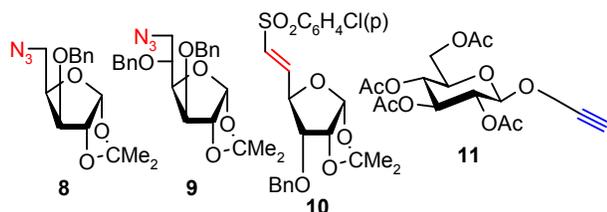
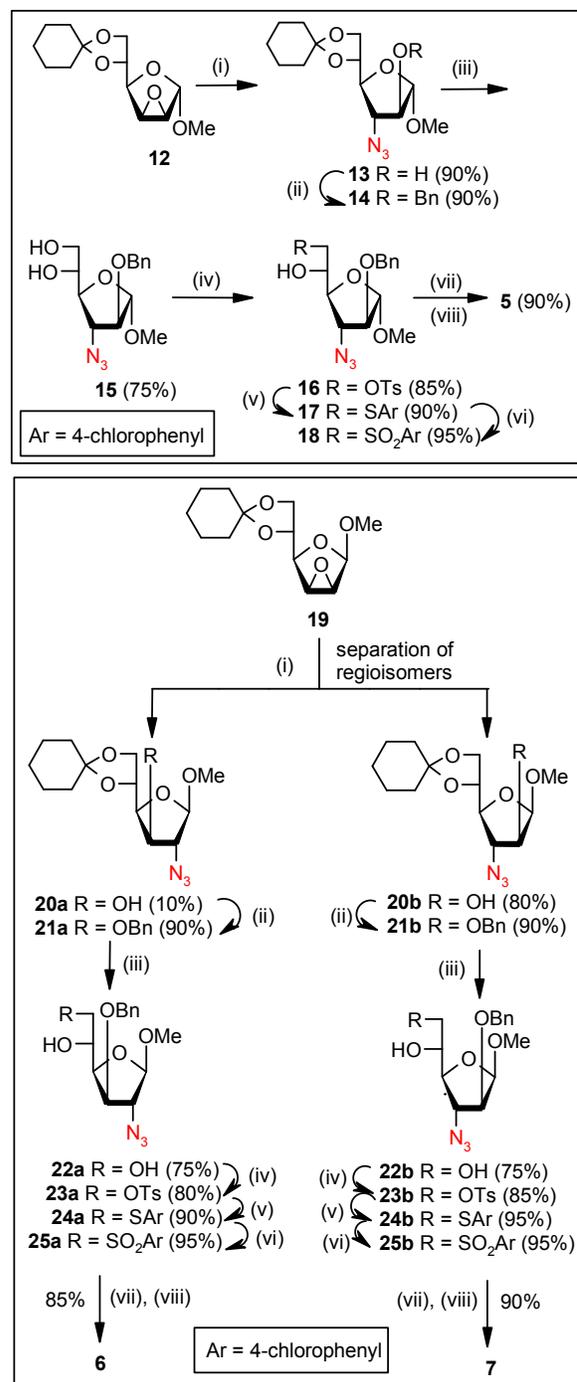


Figure 3: Reactive sugar counterparts for trisaccharide synthesis.

Synthesis of building blocks started with the regioselective opening of the epoxide ring of **12⁸** by azide ion in presence of ammonium chloride in DMF at elevated temperature to obtain **13** which was benzylated with benzyl bromide and NaH in DMF at room temperature to afford **14**. Deprotection of **14** by 80% aqueous acetic acid at 80 °C generated the diol **15** which was selectively tosylated by TsCl in pyridine/toluene mixture at 4 °C to obtain **16**. The C-S bond formation of the tosylate **16** with 4-chlorothiophenol in presence of tetramethyl guanidine (TMG) in DMF at 90 °C for 5 h followed by oxidation of the sulfide **17** with MMPP in MeOH at room temperature afforded the sulfone **18**. Mesylation of the sulfone with MsCl in pyridine and subsequent elimination of the mesylate after refluxing with pyridine for 2 h produced the first building block vinyl sulfone-modified hex-5-eno-azidofuranoside **5** (Scheme 1). A similar strategy was employed for the synthesis of two other building blocks, vinylsulfone-modified hex-5-eno-azidofuranosides **6** and **7**, starting from the epoxide **19** via intermediates **20-25** (Scheme 1).

Although we performed the coupling reactions of monomers under metal free and aqueous conditions, it was obvious that the

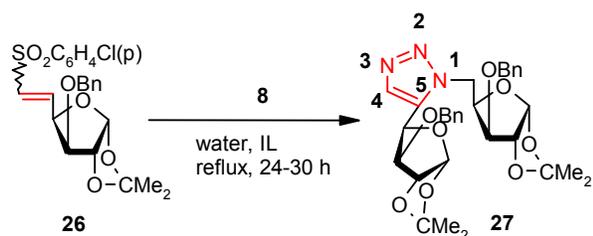
reaction time for the synthesis of most of the 1,5-DT modified carbohydrates reported earlier⁵ specially with the secondary azido groups, was rather long. In heterocyclic synthesis ionic liquids (ILs) were shown to offer advantages over ordinary solvents in terms of increased reaction rates, higher product yields and the possibility of avoiding complex workup procedures.⁹



(i) NaN_3 , DMF, NH_4Cl , 90 °C, 16 h; (ii) BnBr, DMF, NaH, rt, 5-6 h; (iii) 80% aq AcOH, 80 °C, 2.5-3 h; (iv) TsCl, py:PhCH₃ (1:1), 4 °C, 72 h; (v) 4-chlorothiophenol, DMF, TMG, 90-100 °C, 5 h; (vi) MMPP, MeOH, rt, 12 h; (vii) MsCl, py, 0 °C, 24 h, (viii) py, reflux, 2 h

Scheme 1: Synthesis of vinyl sulfone modified azidofuranoside

Moreover, water/IL combinations were reportedly superior¹⁰ to the conventional organic solvents and biphasic IL/solvent systems. Since vinyl sulfones are relatively slower to react with azides, the shortening of reaction time was necessary to synthesize more complex 1,4-DT and 1,5-DT linked homo- and hetero-trisaccharides. Therefore, we studied a model coupling reaction using a group of easily accessible and inexpensive ILs. A group of ILs, N,N-dimethyl ethanol ammonium formate (DAF), N,N-dimethyl ethanol ammonium acetate (DAA) and N,N-dimethyl ethanol ammonium chloride (DAC) were prepared from N,N-dimethyl ethanol amine and the required acids (See SI for preparation). The model compound **27** was synthesized earlier by coupling **26** and **8** in refluxing water.^{5c} We decided to study the formation of **27** by coupling **26** and **8** in aqueous-ILs (Scheme 2) using water/DAF, DAA or DAC (1:1 water:IL). It was evident that the reaction time shortened significantly in aqueous-IL media (Table 1). DAF was found to be the most efficient among the ILs used in this study in terms of the cleaner product formation as well as shorter reaction time and therefore we used DAF for the synthesis of new sets of 1,5-DT-linked disaccharides.



Scheme 2: 1,5-DT linked furanoside-furanoside dimer.

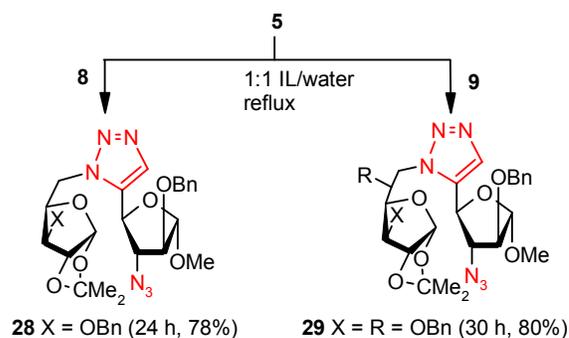
Table 1: Synthesis of **27** using aqueous ionic-liquids

Vinyl sulfone	Azide	Product	Solvent	Reaction time (h)	Yield (%)
26	8	27 ^{5c}	water	42	75
26	8	Do	water-DAF	24	80
Do	Do	Do	water-DAA	30	76
Do	Do	Do	water-DAC	30	78

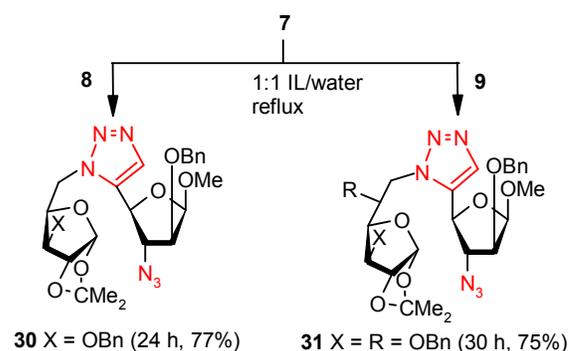
The bifunctionalized building blocks **5**, **6** and **7** were subjected to cycloaddition reactions with the azidosugars **8** and **9** in aqueous DAF (1:1 v/v) under refluxing conditions. Vinyl sulfone **5** reacted with the azidosugars **8** and **9** to afford the 1,5-DT linked- disaccharides **28** and **29** (Scheme 3). On the other hand, between the regioisomeric pair **6** and **7**, only **7** reacted with the azidosugars **8** and **9** to afford the 1,5-DT linked disaccharides **30** and **31** (Scheme 4); compound **6** decomposed under the reaction conditions. It should be noted that building blocks **5-7** did not undergo self-coupling reactions when separately heated under reflux in IL/water mixture.

The reaction of the 1,5-DT **30** with the vinyl sulfone-modified carbohydrate **10** afforded the 1,5-DT linked trisaccharide **32** (Scheme 5) in poor yield; this may be due to a combination of the sluggish nature of vinyl sulfone coupling and the secondary azido group. The disaccharides **28** and **29** were coupled with the known **11** (Figure 3) using CuAAC condition¹¹ to afford the 1,5- and

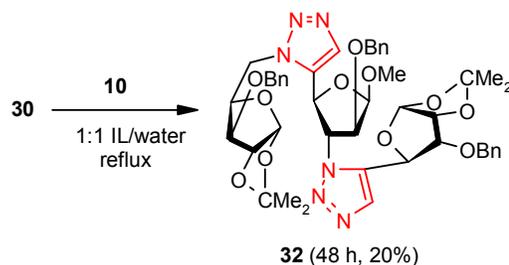
1,4-DT linked trisaccharides **33** and **34** in good yields (Scheme 6). The disaccharides **30** and **31** were coupled with **11** under the



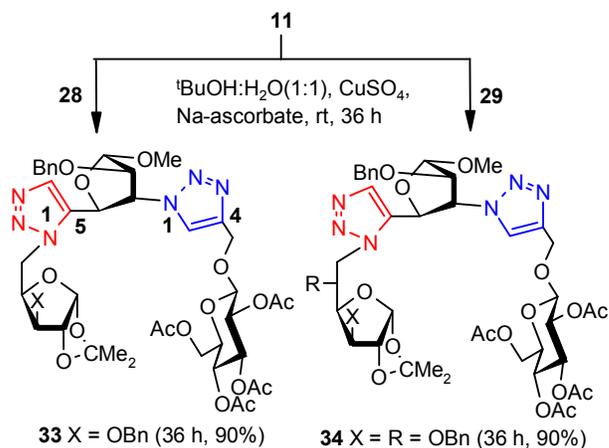
Scheme 3: Synthesis of 1,5-linked disaccharides.



Scheme 4: Synthesis of 1,5-DT linked disaccharides.

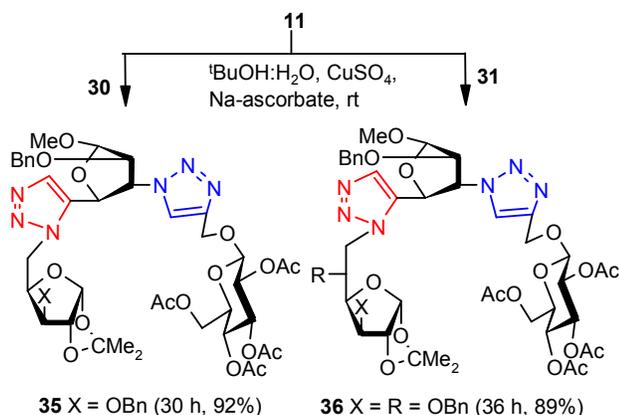


Scheme 5: Synthesis of 1,5-DT linked trisaccharide.



Scheme 6: Synthesis of 1,5- and 1,4-DT linked trisaccharides.

CuAAC condition to afford the 1,5- and 1,4-DT-linked trisaccharides **35** and **36** in good yields (Scheme 7). However the otherwise efficient CuAAC coupling was also slow although the final products were obtained in high yields. The vinyl sulfone **6** was unstable under the reaction conditions and underwent complete decomposition without affording any disaccharide.



Scheme 7: Synthesis of 1,5- and 1,4-DT linked trisaccharides.

A comparison of the chemical shifts of C4 and the quaternary C5 of **28-31** established the regioisomeric nature of triazoles. The C4 and quaternary C5 chemical shift values of **28-31** range between 132.3–134.1 ppm and 134.7–136.9 ppm respectively. The range of difference between these two sets of numbers, $\Delta(\delta_{C4}-\delta_{C5})$ is small and negative (–0.6 ppm to –4.6 ppm). This observation is in agreement with the literature reported strategy to differentiate between 1,4-DTs and 1,5-DTs and thus proved the presence of 1,5-DTs in compounds **28-31**. Similarly the C4 and quaternary C5 chemical shifts of the triazole rings in compound **32** range between 132.8 ppm–134.5 ppm. Therefore $\delta_{C4}-\delta_{C5}$ becomes small and negative¹² which identified only 1,5-DT components. For trisaccharides **33-36**, the difference of C4 (132.6 ppm–134.1 ppm) and quaternary C5 (134.5 ppm–136.5 ppm) chemical shifts is small and negative (–0.5 ppm to –3.8 ppm) and therefore establishes the presence of 1,5-DTs carried forward from disaccharides **28-31**. On the other hand, the difference between the new sets of chemical shifts arising out of the C4 (144.3 ppm–144.6 ppm) and C5 (123.8 ppm–124.1 ppm) in **33-36** is large and positive (+20.3 ppm to +20.8 ppm) and thereby the formation of 1,4-DT linkage is unambiguously established.

In conclusion, a building block approach has been designed by taking advantage of the difference in rates of reactivities of primary and secondary azides of azidosugars. Thus, sugar molecules **6** and **7** decorated with both vinyl sulfone and a secondary azide do not undergo self-coupling but the vinyl sulfone moiety reacts selectively with the primary azide group of an externally delivered sugar molecule to afford four 1,5-DT-linked disaccharides **28-31**. This coupling reaction is carried out in water-IL mixture after a model experiment indicated that the water-IL mixture was superior to pure water. The unreacted azido group of the disaccharide **30** was coupled with a vinyl sulfone-modified carbohydrate in water-IL mixture to get the first ever 1,5-DT-linked homo-trisaccharide **32** albeit in poor yield. The

disaccharides **28-31** were coupled with the propargylated sugar **11** under CuAAC reactions to afford the first ever 1,5-DT and 1,4-DT-linked hetero-trisaccharides **33-36**. Work is in progress to increase the efficiency of coupling under benign reaction conditions to access more complex 1,5-DT linked homo- and 1,5-DT/1,4-DT linked hetero- polysaccharides and to study their properties

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