# First synthesis of 1,2,3-triazolo-linked (1,6)-α-D-oligomannoses (triazolomannoses) by iterative Cu(I)-catalyzed alkyne–azide cycloaddition†‡

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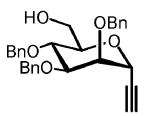
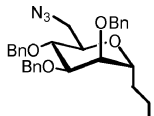
**The iterative copper(I)-catalyzed cycloaddition (rt or microwave) between an ethynyl α-*C*-mannoside and alkyl 6-azido-α-*C*-mannoside derivatives was suited to the (1,6)-ligation between α-D-mannose units through 1,4-disubstituted triazole bridges, thus resulting in the formation of linear oligomers (80–90% yield) with alternating triazole and mannose fragments up to a triazolo-pentamannose derivative.**

The preparation of carbohydrate-based libraries displaying a substantial number of compounds with structural and stereochemical elements of diversity is a basic step in the search for biological, biochemical and biophysical probes in service to glycobiology[1] and in the identification and development of new therapeutics or vaccines against largely diffuse human diseases such as cancer, inflammation, and viral infections.[2] With the current development status of *O*-glycosidation methodology by solution and solid-state chemistry,[3] including sophisticated techniques to increase the reaction efficiency and simplify the product isolation and purification,[4] there is a widespread perception that synthetic glycochemistry is at the stage that permits one to embark on projects toward the construction of *O*-oligosaccharides and *O*-glycoconjugates with high structural complexity. In recent years substantial advancements have also been made in the synthesis of carbohydrate analogues where the glycosidic oxygen atom has been replaced by another atom, functional group, or heteroaromatic ring. Accordingly, *S*-glycosides[5] and *C*-glycosides[6] have been prepared with the main goal of obtaining glycosidase-resistant substrates as probes and inhibitors of critical biological processes. Conversely, acetyleno-oligosaccharides were designed and synthetized[7] as tools for studies on the role of hydrogen-bonding in polysaccharides and in carbohydrate–nucleic acid and carbohydrate–protein systems. The linking of a carbohydrate covalently with another carbohydrate or non-carbohydrate residue through a 1,2,3-triazole ring is also a recent and valuable aquisition.[8] The power of this approach for bioconjugation chemistry in general[9] relies primarily on the facile assembly of the 1,4-disubstituted 1,2,3-triazole ring *via* a chemoselective ligation reaction such as the modern Cu(I)-catalyzed version[10] of the azide–alkyne 1,3-dipolar cycloaddition.[11] Other positive features include the biocompatibility of the reactants due to the orthogonal reactivity of the azido and acetylene groups to those of the functional groups in biological systems and the inertness of the triazole ring to metabolic transformations.[12] Nevertheless, the triazole core is more than a passive linker because it can participate in hydrogen-bonding and dipole interactions, which can favor the binding to biomolecular targets and improve solubility.[8a,13] Within this context, we report on the unprecedented iterative azide–alkyne ligation resulting in the formation of a new class of oligosaccharide analogues displaying the 1,2,3-triazole ring as a rigid and stable linker between α-D-mannose residues (triazolo-oligomannoses). The choice of mannose as the sugar fragment in these oligomers was suggested by their potential use as mimetics of the manno-oligosaccharide family members which constitute the essential substructure of mycobacteria lipoglycans.[2g,14]

The orthogonally-substituted ethynyl α-*C*-mannoside **1** and the alkyl 6-azido-α-*C*-mannoside **2** were designed as the building block and platform respectively in the planned iterative methodology. The use of *C*-glycosides was a prerequisite in our program with the intention of constructing oligomers devoid of *O-glycosidic linkages* and therefore highly resistant to chemical and enzymatic degradation.[15]




**1**




**2**


The acetylene **1** was prepared in two steps and high yield (87%) from the known *O*-perbenzylated ethynyl α-*C*-mannoside.[16] Compound **1** was transformed into **2** (51%) by first converting the ethynyl group into the ethyl methoxymethyl (MOM) ether and then substitution of the primary OH at C-6 with $N_3$. Thus, in the first coupling reaction between **1** and **2** on a 130 mg scale, the best conditions were established by the use of a slight excess of **1** (1.1 equiv.) in the presence of 0.2 equiv. of CuI and 4.0 equiv. of base (*N*,*N*-diisopropylethylamine, DIPEA); the reaction was carried out in toluene at room temperature and went to completion in 10 h. The filtration of the crude product through a short column of silica gel afforded the pure triazolo-dimannose **3** as a single cycloadduct in very good isolated yield (Scheme 1). Then the free hydroxy group in this product was transformed into the azido group by treatment with diphenyl phosphoryl azide (DPPA, 3.0 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.0 equiv.) in dry DMF (120 °C, 20 h). From this reaction the azide **4** was obtained in good yield (Scheme 1) and served as substrate in the subsequent cycloaddition with **1**. The same coupling–azidation sequence was repeated over two more cycles with similar efficiency (see Scheme 1). Also a fourth coupling reaction afforded the corresponding product **9** (triazolo-pentamannose) in good yield

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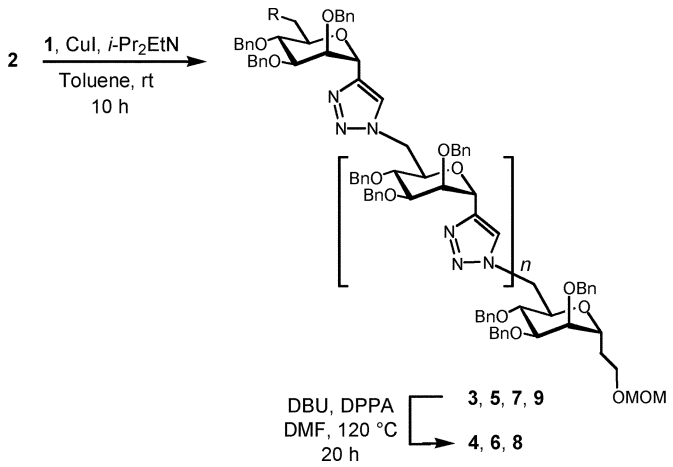
‡ We propose the trivial name of triazolosaccharides for oligosaccharide analogues where the glycosidic oxygen atom is replaced by a 1,2,3-triazole ring.



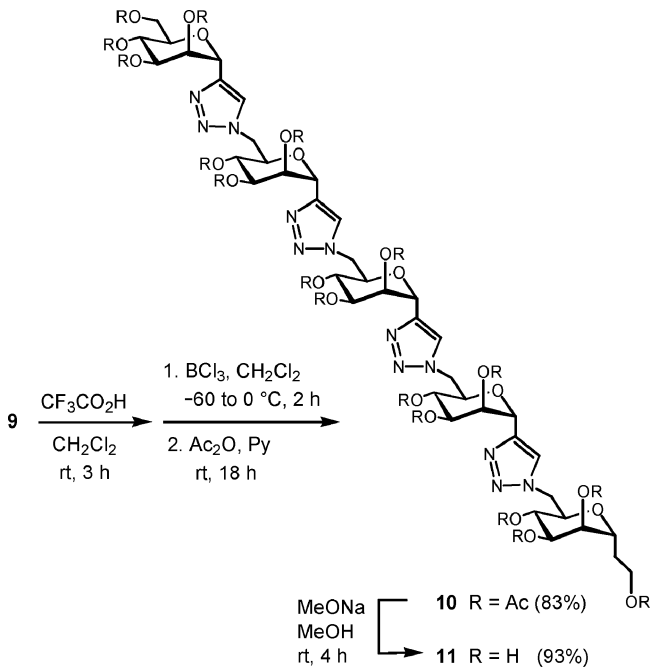

| Cycle | *n* | Coupling Product R = OH | Yield % | Azide derivative R = $N_3$ | Yield % |
|---|---|---|---|---|---|
| 1 | 0 | **3** | 80 | **4** | 81 |
| 2 | 1 | **5** | 87 | **6** | 85 |
| 3 | 2 | **7** | 90 | **8** | 79 |
| 4 | 3 | **9** | 84 | | |

**Scheme 1**

and, therefore, at that stage we considered that the viability of the explored route toward (1,6)-oligomannose analogues with triazole linkers had been sufficiently demonstrated. Apparently, the only disadvantage with this methodology resided with the long reaction time (*ca.* 30 h) to perform the reaction sequence in each cycle effectively. However, this problem was readily circumvented by the use of microwave irradiation at 100 °C for the cycloaddition and 120 °C for the azidation. Under these conditions the reaction time of the first step was reduced to 5 min and that of the second step to 2 h. Quite gratifingly, the yields of isolated products were very close or identical to those registered in the reactions carried out under conventional conditions.

Owing to the presence of a free hydroxy group and the orthogonal protection of the others, the oligomer **9** appears to be well tailored to the need of its selective elaboration into products suitable for insertion into other substrates. However, the transformation of **9** into the *O*-peracetylated derivative **10** and the free hydroxy product **11** was carried out with the intention of demonstrating the tolerance of the heavily protected oligomers toward the elaboration into suitable products for biological tests (Scheme 2). Thus, MOM was first removed from **9** by the action of $CF_3CO_2H$ and all the other hydroxy groups were liberated by debenzylation with $BCl_3$; treatment of the reaction mixture with acetic anhydride afforded **10** in very good yield. A pure sample of the free hydroxy product **11** was obtained by deacetylation of **10** with sodium methoxide. In addition of being an easily manipulable product, compound **10** displayed a $^{13}C$ NMR spectrum that served beautifully for the structural assignment of the four triazole rings. In fact, while the 1,4-disubstitution array was readily established[17] in the first coupling product **3**, we wished to prove unequivocably the occurrence of the azide–alkyne cycloaddition with the *same* regiochemistry over the four consecutive cycles. To our delight this was found to be the case. In fact, driven by an earlier valuable study,[18] the $^{13}C$ NMR analysis of **10** was carried out. The spectrum showed four pairs of signals, one for each triazole ring, displaying large $\Delta(\delta_{C4}–\delta_{C5})$ values (*ca.* 18 ppm). This result corroborated the 1,4-disubstituted structure for all triazole rings since much smaller and even negative $\Delta(\delta_{C4}–\delta_{C5})$ values were expected for 1,5-disubstituted regioisomers.[17,18]

In conclusion we have demonstrated the efficiency and fidelity of the Cu(I)-catalyzed azide–alkyne ligation strategy in an iterative




**Scheme 2**

methodology leading to the new class of (1,6)-oligomannose analogues displaying the triazole ring as a linker. Since the coupling reaction was repeated four times with similar and high levels of efficiency, it is likely that the limit of application of the methodology was not reached. The extension of the scope of this methodology to the synthesis of (1,2)-oligomannose analogues as well as to branched oligomers now becomes of great interest. Also, the performance of the two-reaction iterative protocol by a solid-phase techique eventually in a fully automatized manner will be the subject of further studies.

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