Studies Toward the Synthesis of Inhibitors of *Mycobacterium tuberculosis* Cell-Wall Biosynthesis: The Assembly of Triazole-Linked 1,6-α-D-Oligomannosides via Click CuAAC

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Abstract: A versatile synthesis of 1,6-α-D-oligomannosides featuring the 1,4-disubstituted triazole ring as interglycosidic tether is presented via iterative copper(I)-catalyzed azide–alkyne cycloaddition. Free hydroxy hexamannoside and decamannoside featuring a capping 6-deoxymannose fragment have been prepared and characterized.

Key words: alkynes, azides, copper, cycloadditions, stereoselective synthesis

Among infectious diseases that were believed to be defeated in the last century, tuberculosis (TB) has reappeared in force[1] and in its deadly partnership with HIV/AIDS pandemic is presently a leading cause of mortality in many parts of the world including Western countries. The recrudescence of TB and the widespread antibiotic resistance have strengthened the need for rapid development of new antitubercolar drugs targeting essential functions of its etiological agent, *Mycobacterium tuberculosis*. An ideal TB drug target is the biosynthesis of the mycobacterial cell envelope. This is composed of various glycophospholipids[2] such as phosphatidylinositol mannosides (PIM)[3] that in addition, being important in their own right, may also be hyperglycosylated to form other wall components such as lipomannans (LM) and lipoarabinomannans (LAM).[4,5] These glycolipids all contain a common α-1,6-linked mannoside core as shown in LM (Figure 1). To inhibit the construction of this highly mannosidic species promoted by the abundance of α-1,6-mannosyltransferases in mycobacteria, Watt and Williams have prepared a series of 6-deoxy α-1,6-linked oligomannosides up to tetramers.[6] They suggested that deoxygenation of the 6-position of the oligomannosyl chain should prevent these compounds acting as substrates for the enzymes. Here we report a new approach to more complex and higher 6-deoxy 1,6-α-D-oligomannosides **1** featuring a 1,4-disubstituted triazole ring as an interglycosidic linker[7] (Figure 1). High stability can be foreseen for these oligomers owing to the resistance of anomeric carbon–carbon bond and triazole ring toward chemical and enzymatic degradation.[8] On the other hand, the triazole ring

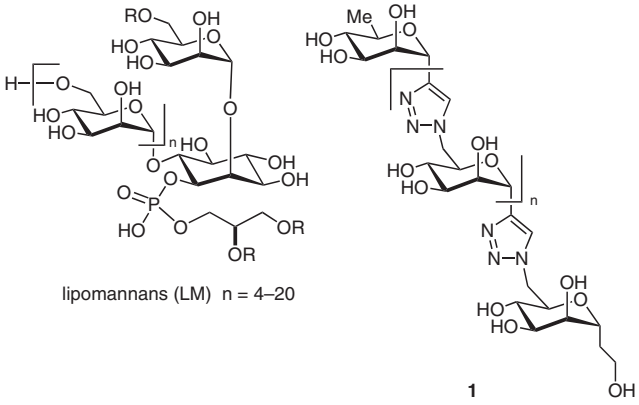

Figure 1 Structures of lipomannans (LM) and designed triazole-tethered oligomannoses (**1**)

can participate in hydrogen bonding and dipole interactions, thereby favoring molecular recognition processes and improving solubility.[9]

To prepare mannose-triazole hybrids **1** we have developed a linear oligomerization strategy based on the click Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC)[10] for linking the mannose fragments. This new synthesis appears more practical than that recently reported from our laboratory,[7,11] as each cycle is constituted of two simple and efficient operations, such as the CuAAC and the unmasking of the ethynyl group in the newly formed oligomer. For the execution of this program, the functionalized new alkynyl mannoside building blocks **2**–**4** (Figure 2) were prepared (see Supporting Information) while the MOM-protected hydroxyethyl 6-azidomannoside **5** (Figure 2) was available in our laboratory from previous work.[7]

With these compounds in hand, the stepwise oligomerization was commenced by the Cu(I)-catalyzed coupling of

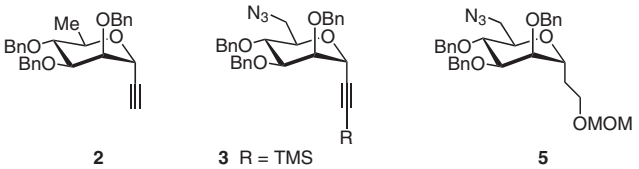

Figure 2 Building blocks for oligomannoside synthesis via CuAAC

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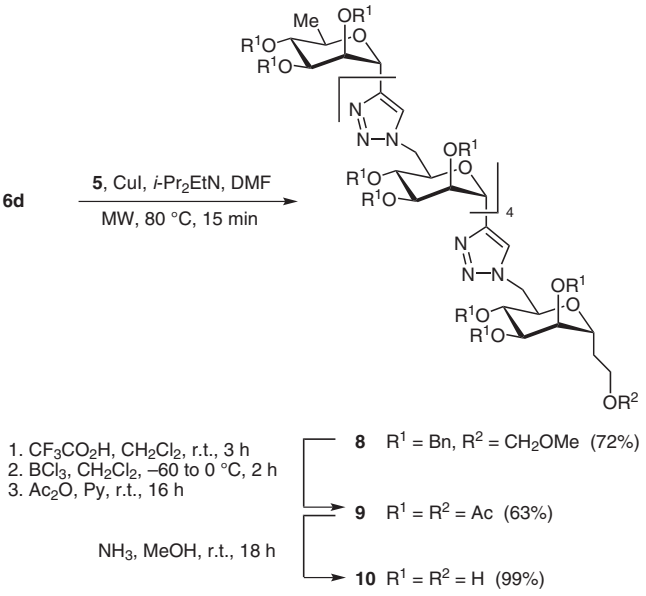
ethynyl 6-deoxymannoside **2** with TMS-ethynyl 6-azido mannoside **3**.

Following the coupling reaction, removal of the TMS group by basic treatment afforded the dimannoside **6a** displaying a free ethynyl group (Scheme 1). Of note, the CuAAC was completed after a short reaction time (15 min under microwave irradiation) while desilylation required one hour. Repetition of the cycloaddition–desilylation reaction sequence over three more consecutive cycles afforded tri-, tetra-, and pentamannosides **6b–d**. Isolated yields of all oligomers prepared and their purity are presented in Scheme 1. Thus, from these data it appears that each coupling product was substantially contaminated by impurities. Very likely, partial desilylation of the major product occurred in each cycle, thereby allowing the formation of higher oligomers. Accordingly, the MALDI-TOF spectrum of **6d** revealed the presence of a hexamannoside. This problem led us to consider the use of 3-hydroxy-3-methylbutynyl 6-azidomannoside **4**, a formal adduct of acetone to ethynyl 6-azidomannoside,[12] as a robust cycloaddition partner in the homologative process. Conditions are known for the removal of acetone (deacetonation) and liberation of the ethynyl group.[13] Thus, the first cycle involved the Cu(I)-catalyzed cycloaddition of **2** with **4** and deacetonation to give the oligomer **6a**. The same reaction sequence was repeated over three more consecutive cycles to give the oligomers **6b–d**. All compounds **6a–d** resulting from this protocol were obtained in excellent yields as well high purities (Scheme 1). Hence, this approach employing **4** appeared to be more efficient than that employing **3**. This was mainly due to the high stability of the 3-hydroxy-3-methylbutynyl group as shown by the harsh conditions required (K_2CO_3 and 18-crown-6 ether in refluxing toluene for 4–8 h) for deacetonation of the individual oligomer formed in each cycle.

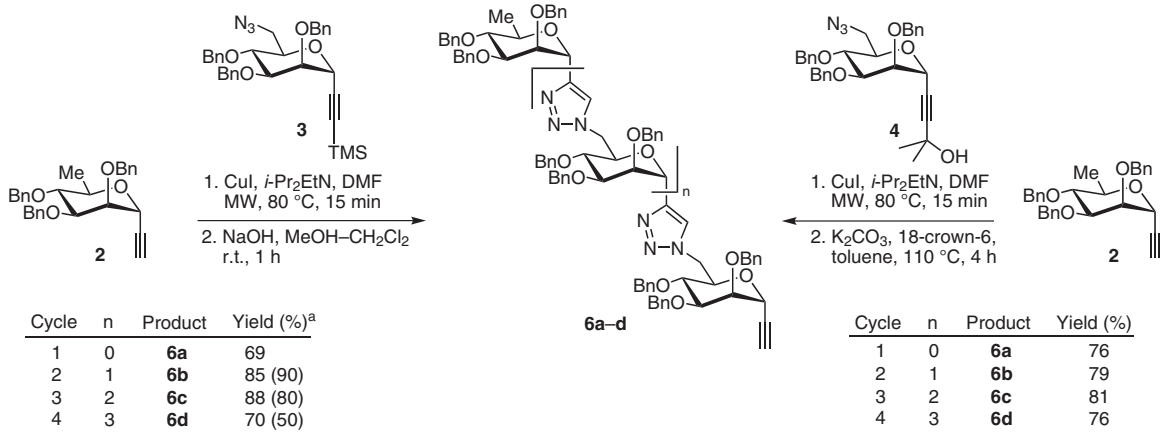
Having secured access to the pentamannoside **6d**, this compound was allowed to react with the capping monomer **5** under microwave-assisted click conditions (Scheme 2) to give the higher oligomer **8** in very good yield (72%). This hexamannoside was submitted to an acid hydrolysis to remove the MOM protecting group and debenzylated by treatment with BCl_3 and MeOH to give



Scheme 2

crude **10** that was isolated as the peracetylated derivative **9** (63% total yield). Then, the removal of the acetyl groups (NH_3 in MeOH) gave pure **10** in almost quantitative yield.

As cell-wall constituents of *Mycobacterium tuberculosis* possess high oligomannose cores, in order to mimic more closely such a structural feature, we set out to transform **6d** into a decamannoside by coupling with the azide-functionalized oligomer **11** (Scheme 3). This azide was prepared by azidation of the corresponding alcohol whose synthesis was reported earlier from our laboratory.[14] Gratifyingly the Cu(I)-catalyzed cycloaddition of these oligomers took place with high efficiency to give the expected higher oligomannose **12** in 93% isolated yield (Scheme 3). Acid hydrolysis of this compound cleaved the acetal group and induced the MOM-group removal. This was followed by ether cleavage by treatment with BCl_3 to achieve all benzyl group removal. Acetylation of the resulting crude material with Ac_2O and pyridine afforded the peracetylated decamannoside **13** that was purified and fully characterized. Finally, deacetylation of **13**



Cycle	n	Product	Yield (%)[a]
1	0	**6a**	69
2	1	**6b**	85 (90)
3	2	**6c**	88 (80)
4	3	**6d**	70 (50)

Cycle	n	Product	Yield (%)
1	0	**6a**	76
2	1	**6b**	79
3	2	**6c**	81
4	3	**6d**	76

Scheme 1 Stepwise oligomerization. [a] Values in parentheses refer to the purity of the isolated compound (^{1}H NMR analysis).

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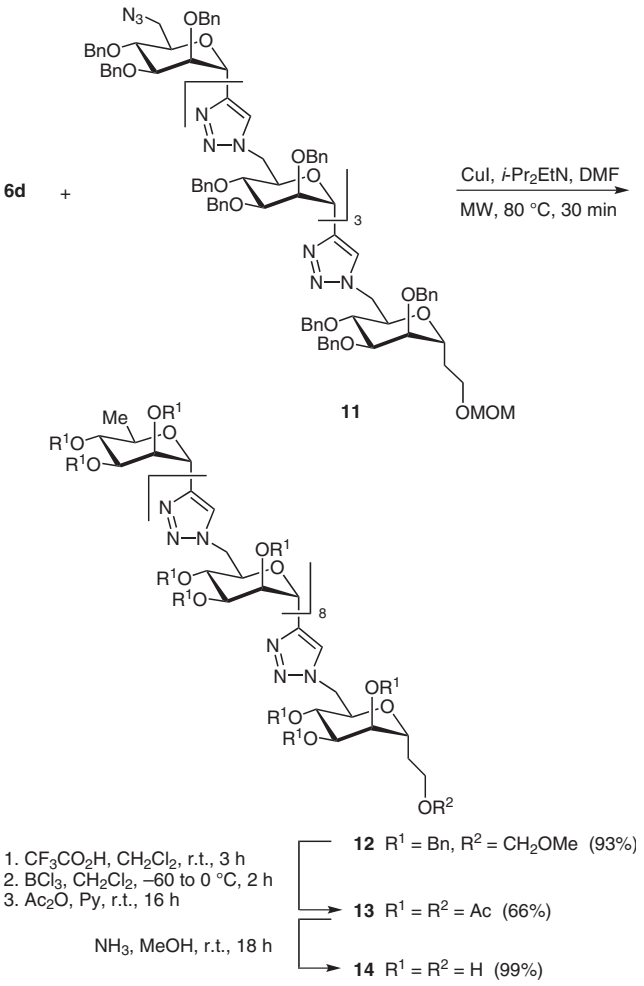

Scheme 3

by 1 M NH_3 in methanol afforded the free hydroxy product **14**.

We believe we have paved the way to a new family of oligomannose mimics that display two main features. One is the interglycosidic triazole ring linked by a carbon–carbon bond to each mannose residue. The second is the presence of a capping 6-deoxymannose fragment in one side of the chain. These features have been designed to make the oligomers stable to enzymatic degradation and unable to undergo mannosyltransferase-promoted glycosylation, the key process for the *Mycobacterium tuberculosis* cell-wall biosynthesis. Consequently, the free hydroxy hexamannoside **10** and decamannoside **14** appear to be interesting substrates worth testing against that bacterium, the etiological agent of tuberculosis. The synthesis of higher homologues is under way, and the biological assays of all the triazole-linked *C*-oligomannosides that have been prepared will be carried out and reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) The building block employed in the earlier synthesis was an ethynyl α-D-*C*-mannoside. Therefore, each cycle was constituted of the click azide–alkyne reaction and then transformation of the 6-hydroxy into azido group in the resulting product.
(12) It has to be noted that attempts to synthesize compound **4** by addition of acetone to ethynyl 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*C*-mannopyranoside failed in our hands. The basic conditions required for this process induced the 1,2-elimination of benzyl alcohol leading to the undesired glycal.
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(14) Compound **9** in ref. 7 was treated with diphenylphosphoryl azide (DPPA) and DBU under microwave irradiation (120 °C, 2 h) to give **11** in 78% isolated yield (see Supporting Information).

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