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Atropisomerism

Efficient Atropodiastereoselective Access to 5,5′-Bis-1,2,3-triazoles: Studies on 1-Glucosylated 5-Halogeno 1,2,3-Triazoles and Their 5-Substituted Derivatives as Glycogen Phosphorylase Inhibitors

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Abstract: Whereas copper-catalyzed azide–alkyne cycloaddition (CuAAC) between acetylated β-D-glucosyl azide and alkyl or phenyl acetylenes led to the corresponding 4-substituted 1-glucosyl-1,2,3-triazoles in good yields, use of similar conditions but with 2 equiv CuI or CuBr led to the 5-halogeno analogues (>71%). In contrast, with 2 equiv CuCl and either propargyl acetate or phenyl acetylene, the major products (>56%) displayed two 5,5′-linked triazole rings resulting from homocoupling of the 1-glucosyl-4-substituted 1,2,3-triazoles. The 4-phenyl substituted compounds (acetylated, O-unprotected) and the acetylated 4-acetoxymethyl derivative existed in solution as a single form (d.r.>95:5), as shown by NMR spectroscopic analysis. The two 4-phenyl substituted structures were unambiguously identified for the first time by X-ray diffraction analysis, as atropisomers with a*R* stereochemistry. This represents one of the first efficient and highly atropodiastereoselective approaches to glucose-based bis-triazoles as single atropisomers. The products were purified by standard silica gel chromatography. Through Sonogashira or Suzuki cross-couplings, the 1-glucosyl-5-halogeno-1,2,3-triazoles were efficiently converted into a library of 1,2,3-triazoles of the 1-glucosyl-5-substituted (alkynyl, aryl) type. Attempts to achieve Heck coupling to methyl acrylate failed, but a stable palladium-associated triazole was isolated and analyzed by ^{1}H NMR and MS. O-Unprotected derivatives were tested as inhibitors of glycogen phosphorylase. The modest inhibition activities measured showed that 4,5-disubstituted 1-glucosyl-1,2,3-triazoles bind weakly to the enzyme. This suggests that such ligands do not fit the catalytic site or any other binding site of the enzyme.

Introduction

Among the variety of available synthetic methods, efficient and nontoxic processes are attracting increasing interest for clear practical and economic reasons and because of health or environmental concerns. In this context, recent years have witnessed the development of a number of coupling reactions following the concept of "click" chemistry.[1,2] The [3+2] cycloaddition reaction between alkyne and azide groups, first investigated by Rolf Huisgen[3,4] and shown to produce regioisomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles, has become extremely popular. Optimization of the reaction conditions has brought a tighter selectivity control and a better understanding of the reaction steps, so that it is now possible to produce preferentially one or the other of the possible regioisomeric disubstituted triazoles.[5] Whereas the reactivity of alkynes and azides opens synthetic possibilities beyond click reactions,[6] it is also possible to produce 1,4,5-trisubstituted triazoles by a number of methods, including the Huisgen reaction.[7] Readily accessible glycosyl azides are precursors of a number of sugar-based 1,2,3-triazoles,[8–12] and the unique reactivity features of the alkyne-azide pair has made them excellent candidates for the construction of elaborated multivalent glycosylated architectures[13,14] and, more generally, for drug development and diverse chemical biology applications.[15–17]

In recent years, we have developed synthetic approaches to carbohydrate-based glycomimetics and, in particular, *C*-glucosyl aryls and *C*-, or *N*-glucosyl heterocycles designed as potential inhibitors of glycogen phosphorylase (GP).[18] Because this enzyme is responsible for the depolymerization of glycogen, which is the polymeric storage form of glucose, it plays a crucial role in the metabolism of a number of living species. In

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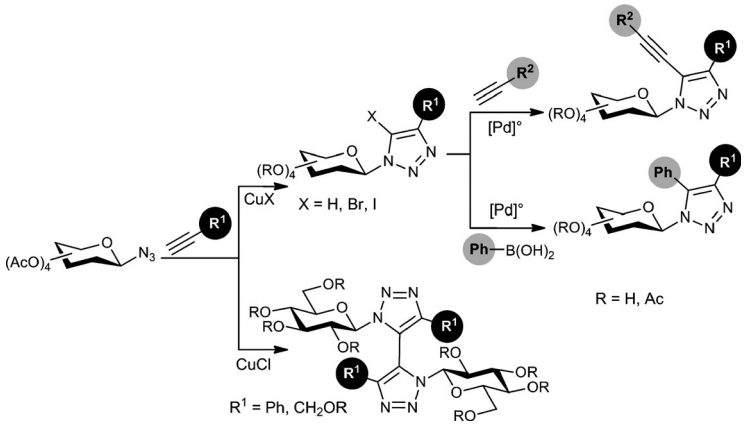
humans, GP has been recognized as a possible pharmaceutical target for pharmacological antidiabetic therapies and is receiving considerable attention.[19,20] Detailed structural studies have revealed five binding sites, which accommodate specific types of ligands. Glucose-based inhibitors usually bind at the catalytic site. In this family, those that display a 2-naphthyl moiety appear to be among the best inhibitors of GP (Figure 1, **A**–**E**). Interestingly, 1-glucosyl-4-hydroxymethyl-1,2,3-triazole **F** also showed good inhibitory properties. Clearly, strict control of the alkyne-azide click reaction selectivity is essential to obtain carbohydrate-based 1,2,3-triazoles that bind tightly at important sites on the protein (e.g., active, allosteric), when designed as pharmacophores for biological or health applications and, in particular, as potential antihyperglycemic drugs.

Recently, syntheses of 1,2,3-triazoles based on carbohydrates of the D-*xylo*[21] and D-*gluco* series[22] were reported under conditions involving copper halide catalysis.[9,11–13] Interestingly, performing the 1,3-dipolar cycloaddition of azide and alkyne using a twofold excess of Cu^{I} halide[22] (CuX, X = Br, I) favored the formation of the 5-halogenated 1,2,3-triazoles. In contrast, when carried out in the presence of CuCl, the click reaction led to a totally different outcome because the main product was a symmetrically 5,5′-coupled bis-triazole that was identified by crystallographic analysis[22] as an a*R* atropisomer (Scheme 1). Similar results were observed when the Huisgen reaction was performed with 5% CuCl and a polysiloxane-supported secondary amine,[23] or when a ribofuranosyl azide and various acetylenes reacted in the presence of CuBr and NaOEt under a dry air atmosphere.[24] Atropisomerism, which is a characteristic feature of a number of natural products, can be critical for determining structure, properties, and bioactivities,[25] and the binaphthyl (BINAP) moiety has high industrial interest.[26] In this context, we present here full data on other bis-triazole atropisomers and further synthetic work towards 5-alkynyl and 5-phenyl substituted 1,2,3-triazoles generated through Sonogashira and Suzuki couplings. Moreover, an evaluation of O-unprotected molecules of this type as rabbit muscle glycogen phosphorylase (RMGP*b*) inhibitors is reported.



Scheme 1. Schematic route to glucosylated 1,4,5-trisubstituted triazoles through CuAAC and subsequent Pd-catalyzed cross-couplings with alkynes (Sonogashira) or phenyl boronic acid (Suzuki) as well as formation of 5,5′-linked bis-triazole atropisomers (see Figure 2 for more detailed representations).[22]

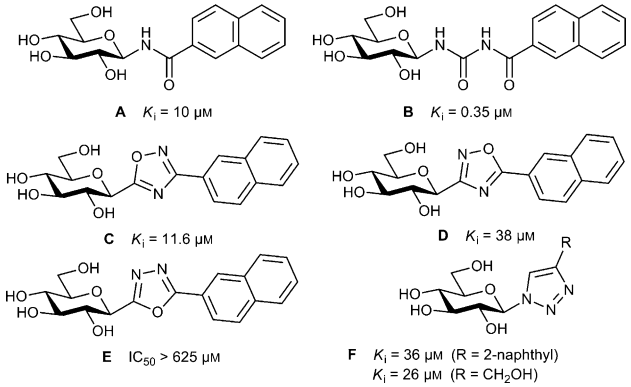
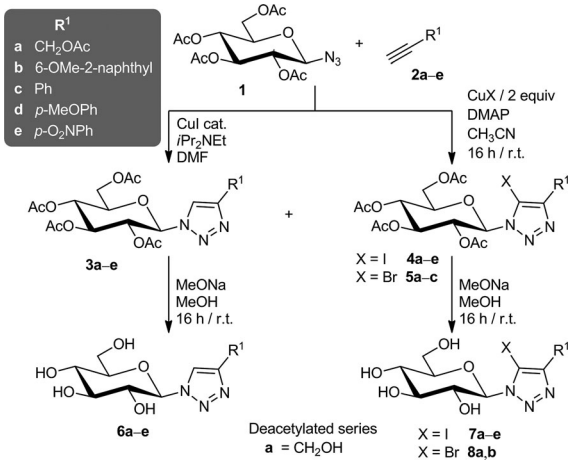


Figure 1. Structures and inhibitions of glucose-based inhibitors of GP displaying 2-naphthyl or 4-hydroxymethyl-1,2,3-triazole moieties (K_i values measured against RMGP*b* for **A**,[27] **B**,[28] **C**,[29,30] **D**,[30,31] **E**,[30] and **F**[32,33]).

Results and Discussion

Glucosyl triazoles **3a** and **3c** (acetylated), and **6a** and **6c** (O-unprotected) are known compounds (Scheme 2) that have been investigated as GP inhibitors.[32] X-ray diffraction analysis of enzyme-inhibitor complexes showed that **6a** ($R^1 = CH_2OH$) and **6c** ($R^1 = Ph$), and its analogues ($R^1 =$ 1-naphthyl and 2-naphthyl), bind at the catalytic site of GP.[32] In the bound state, with the glucose moiety and the aryl residue accommodated in the glucose site and in the β-pocket, respectively, the triazole ring was roughly perpendicular to the glucosyl ring, with the three nitrogen atoms located in the α-side. In the present study, related representatives were prepared from azide **1** and alkynes **2b**, **2d**, and **2e** by copper-catalyzed azide–alkyne cycloaddition (CuAAC) [10 mol% CuI, *N*,*N*-dime-



Scheme 2. Synthesis of 4-substituted *N*-glucopyranosyl-5-halogeno-1,2,3-triazoles through 1,3-dipolar cycloaddition/halogenation.[22]

thylformamide (DMF), 110 °C, 1 h] in the presence of *N*,*N*-diisopropylethylamine (DIPEA; 7.5 equiv). The corresponding triazoles **3b**, **3d**, and **3e** were obtained in 98, 95, and 92% yield, respectively, and the O-unprotected products **6b**, **6d**, and **6e** were obtained quantitatively under Zemplén conditions.

Synthesis of 5-halogenated 1,2,3-triazoles

Syntheses of 5-halogenated 1,2,3-triazoles have been reported starting either from the corresponding 1-halogeno-alkynes[34–39] or from alkynes[40–43] through halogenation of the triazole formed by CuAAC. In the latter case, a stoichiometric source of halide was required, which was provided by Cu^{I}-halides,[42,44] ICl,[40,43] I_2,[40,41,43] or *N*-halogenosuccinimides.[41] This topic has recently been receiving increasing attention.[45] In keeping with these data, we have recently reported the synthesis of glucose-based 5-iodo and 5-bromo 4-phenyl-1,2,3-triazoles (Scheme 2) from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **1** and phenyl acetylene, by using a twofold excess of either CuI or CuBr. In contrast, the synthesis of the 5-chloro 4-phenyl-1,2,3-triazole analogue was less selective (Scheme 3), affording a 5-alkynylated adduct and a dimeric species, formed by oxidative Huisgen coupling, as the major reaction products.[22]

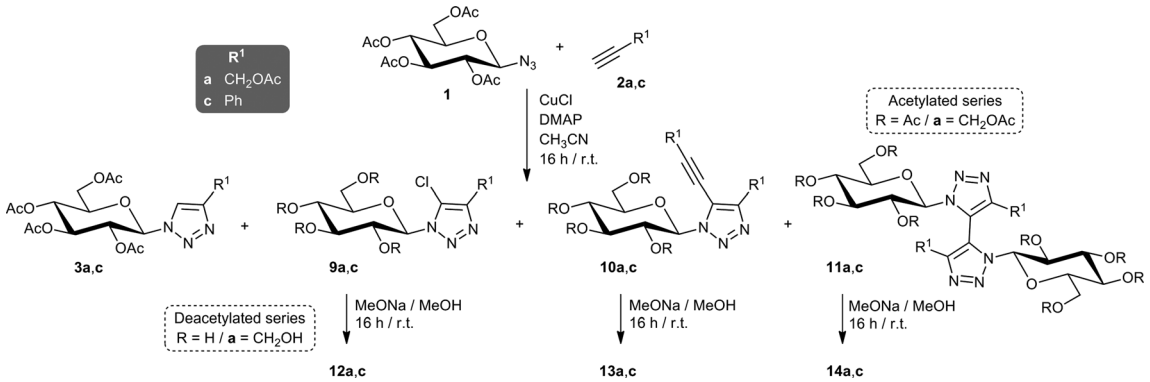
The rapid access to 5-halogenated triazoles through CuAAC provided an opportunity to construct a library of GP inhibitors. Propargyl acetate (**2a**) was selected because of the potent GP inhibition observed with the O-unprotected derivative **6a**[32,33] (Figure 1, **F**). For the same reason, commercially available 6-methoxy-2-naphthyl-acetylene (**2b**) was used to introduce the 2-naphthyl moiety often found in potent glucose-based GP inhibitors (Figure 1, **A**–**E**). Alkynes **2c**–**e**, with a *para*-substituted phenyl ring, offered the opportunity to study the structure-activity relationship toward GP inhibition. Moreover, the use of CuCl allowed atropodiastereoselective access to 5,5′-bis-triazoles. Based on these preliminary findings, the 1,3-dipolar cycloaddition of glucosyl azide **1** with alkynes **2a**–**e** in the presence of a stoichiometric amount of Cu^{I}-halide and catalytic *N*,*N*-dimethyl-4-aminopyridine[42] (DMAP) delivered the 5-iodo-, and 5-bromo-1,2,3-triazoles **4a**–**e** and **5a**–**c**, respectively (Scheme 2).[22] To reach high yields of either **4a**–**e** (>82%) or **5a**–**c** (>71%) (Table 1), use of an excess of copper halide (2 equiv CuI or CuBr) and dilute solutions (ca. 25 mM final concentration in alkynes) were required, thus confirming the critical influence of concentration.[42] To this end, the alkynes dissolved in acetonitrile were added into the reaction medium by using a syringe pump over 16 h. A collection of 5-iodo and 5-bromo 1,2,3-triazoles with alkyl and aryl substituents attached to the 4-position was prepared. The yields recorded for the 5-iodo-triazoles **4a**–**e** were higher by ca. 10–15% compared with those for the 5-bromo-derivatives **5a**–**c**. In both series, as glucosyl azide **1** was converted quantitatively into 5-proto and 5-halogeno triazoles, the corresponding 5-proto-triazoles **3a**–**e** were isolated as byproducts (ca. 20%). Compounds **3b**, **3d**, **3e**, **4a**–**e**, **5a**, and **5b** were deprotected under Zemplén conditions to afford the O-unprotected compounds **6b**, **6d**, **6e**, **7a**–**e**, **8a**, and **8b**, respectively, as potential GP inhibitors.[32,33]

Table 1. Synthesis of 5-halogeno-1,2,3-triazoles with CuI or CuBr in excess.[a]

Alkynes	CuX	Product	Yield [%][b]
2a	CuI	**4a**	86
2b	CuI	**4b**	84
2c	CuI	**4c**	82
2d	CuI	**4d**	82
2e	CuI	**4e**	85
2a	CuBr	**5a**	72
2b	CuBr	**5b**	71
2c	CuBr	**5c**	74[c]

[a] Reaction conditions: Glucosyl azide **1** (1 equiv), alkyne **2a**–**e** (2 equiv), CuX (2 equiv), DMAP (0.3 equiv). [b] Isolated yield of 5-halogeno-1,2,3-triazole **3**–**4**; the difference in the material balance corresponded to 5-proto triazoles **3a**–**e**. [c] See Ref. [22].

Use of similar conditions for the formation of the 5-chlorinated 1,2,3-triazoles (Scheme 3, Table 2) changed completely the outcome of the cycloaddition because the reaction afforded four different products with only minor amounts of the expected chlorinated derivatives **9a** and **9c** (<10%) along with the inseparable 5-proto-triazoles **3a** and **3c** (<20%), and 5-alkynyl-1,2,3-triazoles **10a** and **10c** (<20%), with the dimeric products **11a** and **11c** being isolated as the major component (>55%). The yields for the latter two compounds were rather uniform, and were independent of the alkyl or aryl nature of



Scheme 3. Unexpected outcome for the attempted preparation of 5-chloro-1,2,3-triazoles by using CuCl (2 equiv).

Table 2. Distribution of products formed in the attempted synthesis of 5-chloro-1,2,3-triazoles.[a]

Alkyne	Yield [%][b]			
	3[c]	**9**[c]	**10**	**11**
2a	15	5	19	61
2c	19	9	16	56

[a] Reaction conditions: Glucosyl azide **1** (1 equiv), alkyne **2a**,**c** (2 equiv), CuCl (2 equiv), DMAP (0.3 equiv). [b] Isolated yield. [c] Compounds **3** and **9** displayed similar polarities and could not be separated by silica gel chromatography. The yields were calculated from the integrations measured in the ^{1}H NMR spectrum of the mixture.

the R^1 group. The formation of compounds related to **10** and **11** was previously observed in only a few cases.[37,46–48] Compounds **9**–**11a**,**c** were deacetylated under Zemplén conditions to afford the corresponding O-unprotected glucose-substituted triazoles **12**–**14a**,**c**.

The relative orientation of the glucose and triazole rings in the acetylated 4-acetoxymethyl analogues with different substituents at C-5 (X = H, I, Br, Cl) in **3a**, **4a**, **5a**, and **9a** could be inferred on the basis of the H-1 and H-2 NMR chemical shifts of samples in $CDCl_3$. Whereas the H-1 signals all resonate near 5.8 ppm, the chemical shifts for H-2 were found at ca. 5.40 (**3a**, X = H), 5.90 (**9a**, X = Cl), 5.95 (**5a**, X = Br), and 5.99 ppm (**4a**, X = I), demonstrating the influence of the nearby halogen atom. This supported the conclusion that in 5-proto and 5-halogeno 1-glucosyl triazoles the nitrogen atoms are found on the α face associated with the glucosyl ring.

Acetylated bis-triazole **11c**, which was shown by ^{13}C NMR to display a single form (> 95:5) in the solution state,[22] was analyzed by X-ray crystallography and found to correspond to a single atropisomer with an a*R* stereochemistry along the C-5–C-5′ bond between the triazole rings. The dihedral angle around the C-5–C-5′ bond was $\psi \approx 90^\circ$, with the phenyl rings and the triazole moieties being coplanar in the solid state, $\omega \approx 0^\circ$ (dihedral angles are shown in Figure 2). These observations represent an unprecedented case of complete stereoinduction[23,24,46,49] for a synthesis yielding a single atropisomer by homocoupling of chiral sugar-substituted triazole units. The O-unprotected derivative **14c**, which was also amenable to crystallization, was analyzed by X-ray crystallography (Figure 2; CCDC-926241); the results revealed that the compound was a single atropisomer in the crystal structure, again with a*R* stereochemistry along the C-5–C-5′ bond joining the triazoles. In **14c**, the two triazole rings were tilted with a dihedral angle $\psi = 104^\circ$ (Figure 2a). The unmasking of the hydroxyl groups resulted in a $\omega \approx 25^\circ$ tilt of the phenyl rings to the triazoles. Compounds **11c** and **14c** shared common features: a) The overall geometry of the glucopyranosyl rings corresponded to an usual $^4C_1$ chair conformation, as also shown by the coupling constants in the ^{1}H NMR spectra; b) Identical conformations along the *N*-glucosidic bond, placing the C-1–O-5 bond in a perpendicular direction to the triazole ring, with the anomeric proton roughly eclipsing the vicinal triazole ring, probably as a result of stereoelectronic effects and minimized steric hindrance; c) In contrast to the orientation generally noted for

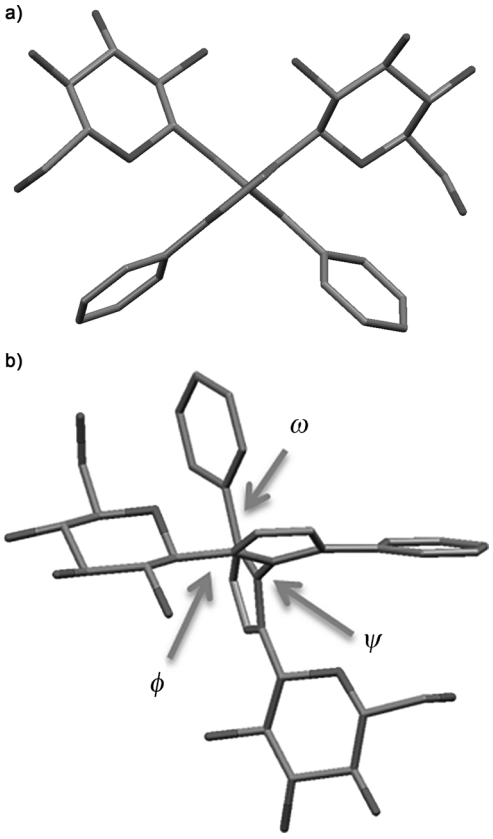


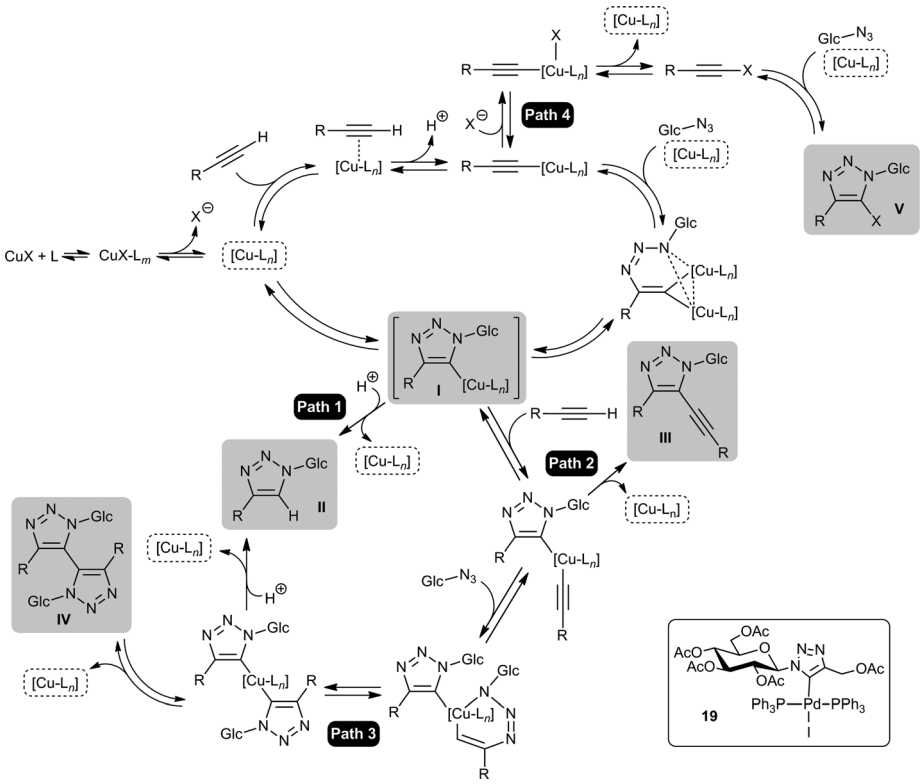
Figure 2. Crystallographic structure obtained for compound **14c**. a) View from the axis following the C–C bond between the C5 carbon atoms of the 1,2,3-triazoles; the C2 axis is a vertical line perpendicular to the C–C bond. b) Alternative view displaying the triazole rings in a different orientation. Dihedral angles Φ (O5-C1-N1-N2), ψ (triazole/triazole), ω (triazole/phenyl) are indicated.

4-substituted 1-*N*-glucosyl-1,2,3-triazoles and other 5-substituted (halogen, alkyl, aryls) analogues (as discussed above for **3a**, **4a**, **5a**, and **9a**), the three nitrogen atoms N1-N2-N3 lay on the β face associated with the nearby glucosyl ring, whereas the C-5–C-5′ bis-triazole junction was positioned on the α face; d) The 6-OAc and 6-OH glucose groups (the planar disposition of the C-5-C-6-OAc group is clearly visible for **11c**) are located close to a phenyl ring lying in a roughly parallel orientation, so that one C-6–H bond (and apparently the O-6–H bond in **14c**) points towards the center of the nearby phenyl ring attached to the distal triazole ring. Accordingly, ^{1}H NMR data displayed the diastereoisotopic methylene protons (δ = 3.88 and 3.14 ppm, for H-6a and H-6b in **11c**, with one notably shielded) as an AX system instead of the AB system usually observed (and visible near 4.0 ppm for **11a**). A C2 axial symmetric structure was observed in crystalline **11c** and **14c**. In addition to **11c** and **14c**, which adopted a single conformation in solution and in the solid state, **11a** also existed as a single atropisomer in $CDCl_3$ as judged by NMR spectroscopic analysis. In contrast, deacetylated compound **14a** gave rise to 18 carbon signals (ca. 3:2 ratio) in its ^{13}C NMR spectrum recorded in [D_4]MeOH (and also a complex ^{1}H NMR spectrum; see the Supporting Information), thus suggesting the presence of two spe-

cies in the solution. In another study,[23] among a number of 1,4-disubstituted 1,2,3-triazoles and bistriazoles prepared by the Huisgen reaction carried out with 5% CuCl and a polysiloxane-supported secondary amine, compound **11c** was obtained in modest yield (32%) as a 85:15 diastereoisomeric mixture. The axial chirality was not determined, but the similarity of the reported NMR data with ours strongly suggest an a*R* configuration in the major species. The ribofuranosyl-based bistriazoles reported were apparently obtained as single species, as judged from the NMR data provided, but their axial chirality was not established.[24]

Whereas the presence of the acetyl protective groups and/or the phenyl rings in **11a**, **11c**, and **14c** resulted in more bulky structures, thus restricting rotation around the C–N glycosidic bonds (Figure 2b), reduced hindrance in O-unprotected **14a** opened possibilities of rotation, along either the *N*-glucosidic bond or the 5,5′-link between the triazole rings, with variations of the Φ and Ψ dihedral angles. Considering the preferred conformation observed for simple glycopyranosyl triazoles,[32] rotation of the glucopyranosyl ring along the *N*-glycosidic bond can be assumed, although it would lead to severe steric interactions. Moreover, should rotation involve one or the other carbohydrate moieties, more complex spectra are to be expected as a result of the different environment around each glucose moiety. Change from an a*R* to an a*S* chirality along the 5,5′ bis-triazole link is a more probable event. In effect, solvent-dependent atropisomerism has been reported for the natural product FD-594 (with a 9,10-dihydrophenanthren skeleton) and analogues, for which the influence of intramolecular hydrogen bonds was crucial. It was concluded that their axial chirality can be controlled by the choice of solvent ($CDCl_3$, $[D_4]$MeOH, $[D_8]$toluene).[50] Whereas the barrier of rotation of biaryl systems is lowered when they are bridged by a six-membered ring, bis-triazoles should rotate more easily than biaryls because of their smaller size. The C2 axial symmetric structure observed in crystalline **11c** and **14c** with a*R* chirality, and assumed for **11a** in solution, may be altered in basic methanol during the deacetylation step to give **14a**. Attempts to promote rotation on heating the $[D_4]$MeOH solution (up to 55 °C) so as to reach coalescence, did not result in a simplification of the NMR spectrum. Larger chemical shift variations (Δ) were observed in the ^{13}C NMR spectra for signals at $\delta = 123$ (0.78), 88 (0.73), and 73 (1.04) ppm, assigned respectively to C5 (triazole), C1 (anomeric carbon), and C2 (glucose), whereas the anomeric H-1 proton appears as two doublets (δ ca. 5.36 ppm in ca. 3:2 ratio) in the ^1H NMR spectrum. On the basis of these observations, we conclude that a second species appeared as a result of rotation around the 5,5′-bis-triazole bond, thus yielding a diastereomeric atropisomer with a*S* axial chirality.

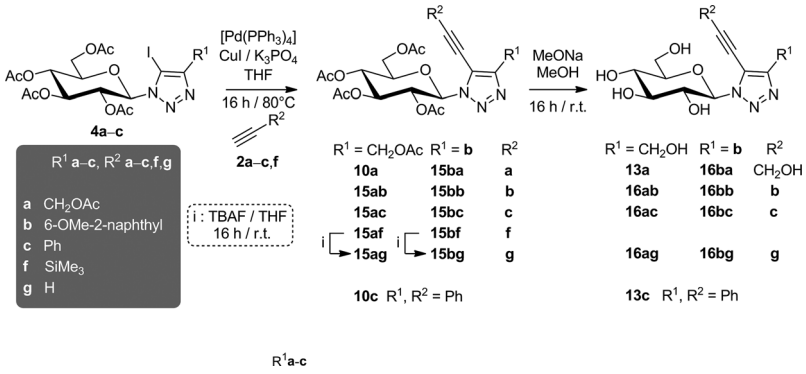
Following ongoing discussions on the azide–alkyne cycloaddition mechanism[5,35,51–57] and its recent elucidation by Valery Fokin et al.,[58] the formation of the four cycloadducts **II**–**V** can be explained by the mechanism outlined in Scheme 4. The initial step is the activation of Cu^I-halides as their activated $[Cu\text{-}L_n]$ species. Chelation of an alkyne then occurs through



Scheme 4. Proposed mechanism for the formation of 5-proto- (**II**), 5-alkynyl- (**III**), or 5-halogeno-1,2,3-triazoles (**V**), and dimeric 1,2,3-triazoles **IV**,[35,48,58] and putative structure of the stable palladium-associated glucosyl triazole **19** isolated in attempted Heck couplings.

π-complexation, and DMAP (the base used) deprotonates the π-alkyne complex to generate a σ-alkynyl complex. The reaction of acetylated glucosyl azide (**1**, Glc-N_3) can create a bis-chelated copper intermediate, which undergoes cyclization to afford 1,2,3-triazole intermediate **I** with a copper σ-complex at the 5-position. The usual evolution of intermediate **I** is through protonation (Path **1**, Scheme 4) to afford 1,4-disubstituted 1,2,3-triazole **II**, as observed in most CuAACs. The copper atom present in σ-complex **I** can coordinate a second molecule of alkyne (which is used in excess) probably through π-complexation followed by formation of a σ-complex, as mentioned previously. This new intermediate can then evolve into 5-alkynylated 1,2,3-triazole **III** (Path **2**) through reductive elimination of

[Cu-L_n]. Paths **2** and **3** involve oxidative Huisgen coupling reactions. On the other hand, if a new molecule of Glc-N_3 is brought into the coordination sphere of the copper atom, a six-membered ring intermediate can be created, which can form a bis-triazolyl-Cu^I σ-complex, from which a dimeric triazolyl species **IV** can be obtained through reductive elimination (Path **3**), but also two molecules of the 5-protonated triazole **II** can be generated as a result of protonation. The protonation steps in Path **1** and Path **3** are therefore critical for the optimal formation of the 5-protonated triazoles **II** under most of the conditions presented in the literature. Similarly, the structure of the bis-triazolyl-Cu^I σ-complex probably largely determines the structure of bis-triazole **IV**.



Scheme 5. Pd-catalyzed Sonogashira cross-couplings with 5-iodo-1,2,3-triazoles.

When an excess of cupper(I) halide (CuX) is used, halogenation of the alkyne becomes prevalent (Path **4**) and the rate of 1,3-dipolar cycloaddition of azides to halogenated alkynes (C≡CX) predominates. The use of CuI and CuBr typically provided the 5-halogenated triazoles **V** as the main products.[22,45] In contrast, chlorination of the alkyne position in Path **4** is probably much slower than the cycloaddition cascades through Paths **1**–**3** because the coordination of chloride to copper is much weaker than for bromide or iodide.[59] The major compounds isolated under chlorination conditions are therefore derivatives **II**–**IV**.

As discussed above, compounds **11a** and **11c** are produced via hindered copper-associated glucosyl-triazoles, and it is reasonable to assume that the preferred conformation around the *N*-glucosidic bond minimized the existing steric interactions between the glucopyranose ring and the complexed copper atom. To this end, the smaller group (anomeric proton) should be directed toward the copper atom in the intermediates along Path **3** in the reaction (Scheme 4). When dimerization occurred to produce acetylated bis-triazoles, probably for kinetic and steric reasons, the conformation of the *N*-glucosidic bond remained unchanged.

Synthesis of 5-alkynyl-1,2,3-triazoles through Pd-catalyzed Sonogashira cross-couplings

The convenient access to 5-halogeno-1,2,3-triazoles **3**, **4**, and **9** paved the way for a study of Pd-catalyzed cross-couplings under Sonogashira conditions with alkynes[60] (Scheme 5), or under Suzuki conditions with aryl boronic acids.[34,36,60]

Application of the standard Sonogashira conditions tested initially (Table 3, entry 1) afforded the desired cross-coupling product **15** in only 20% yield, whereas the reduced product **5** represented ca. 80% yield. Changing the base from triethylamine to potassium phosphate and using [$Pd(PPh_3)_4$] instead of [$PdCl_2(PPh_3)_2$] afforded the desired 5-alkynyl-1,2,3-triazoles **15** in significantly improved yields, along with a small portion of the reduced products **5** (Table 3). The reaction was performed with three 5-iodo-1,2,3-triazoles **4a**–**c** and four alkynes **2a**–**c** and **f**, and afforded a collection of nine 5-alkynyl-1,2,3-triazoles **15**. The yields obtained were good to excellent, except for the cross couplings with propargyl acetate (**2a**; entries 3 and 7). Methanolysis of the acetyl protecting groups afforded the O-unprotected glucose-based 1,4,5-trisubstituted 1,2,3-triazoles **16** in good yields.

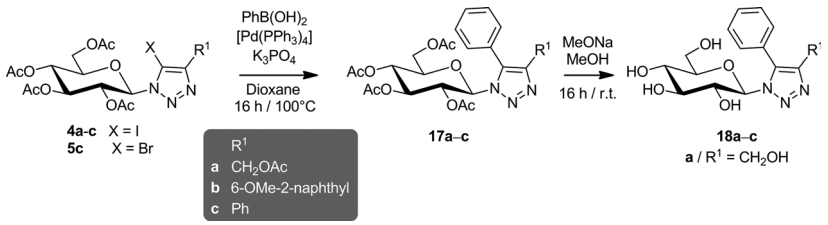
Table 3. Synthesis of 5-alkynyl-1,2,3-triazoles **15**.[a]

Entry	R^1	Alkyne (R^2)	Product	Yield [%][b]
1[c]	Ph	Ph	**15cc**	20
2	Ph	Ph	**15cc**	93
3	CH_2OAc	CH_2OAc	**15aa**	49
4	CH_2OAc	6-OMe-2-naphthyl	**15ab**	86
5	CH_2OAc	Ph	**15ac**	87
6	CH_2OAc	$SiMe_3$	**15af**	73
7	6-OMe-2-naphthyl	CH_2OAc	**15ba**	45
8	6-OMe-2-naphthyl	6-OMe-2-naphthyl	**15bb**	71
9	6-OMe-2-naphthyl	Ph	**15bc**	92
10	6-OMe-2-naphthyl	$SiMe_3$	**15bf**	72

[a] Reaction conditions: 5-Iodo-1,2,3-triazole **4a**–**c** (1 equiv), alkyne **2a**–**c**,**f** (2 equiv), CuI (0.1 equiv), [$Pd(PPh_3)_4$] (0.05 equiv), K_3PO_4 (1.1 equiv). [b] The value indicated is the isolated yield of 5-alkynyl-1,2,3-triazole **15** and the remaining material was composed of 5-proto triazoles **3**. [c] 5-Iodo-1,2,3-triazole **4c** (1 equiv), alkyne **2c** (2 equiv), CuI (0.1 equiv), [$PdCl_2(PPh_3)_2$] (0.05 equiv), Et_3N (1.1 equiv).

Synthesis of 5-aryl-1,2,3-triazoles through Pd-catalyzed Suzuki cross-couplings

The conditions reported in the literature[34,36,60] for Suzuki cross-couplings on a triazole ring (Scheme 6) are very diverse and the efficiency of the coupling reactions seem to be substrate-dependent, with a marked influence of the steric hindrance at the halogenated carbon atom. In the present study, several coupling conditions were therefore evaluated by using 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-phenyl-5-iodo-1,2,3-triazole (**4c**) for optimization (Table 4). The major compound isolated was 5-proto-triazole **3c** when [$PdCl_2(PPh_3)_2$] was used (Table 4, entries 1–5). Zask et al.[61] reported that alkoxide bases react with halogenated aryls in the presence of palladium to provide the reduced aromatic derivatives, as we



Scheme 6. Pd-catalyzed Suzuki cross-couplings with 5-halogeno-1,2,3-triazoles.

Table 4. Synthesis of 5-phenyl 1,2,3-triazole **17c** from 5-iodo derivative **4c**.[a]

Entry	Catalyst (0.1 equiv)	Base (2 equiv)	Solvent	Temp [°C]	**17c**/**3c**[b]
1	$[PdCl_2(PPh_3)_2]$	*t*BuOK	Dioxane	100	28:72
2	$[PdCl_2(PPh_3)_2]$	*t*BuOK	Dioxane	100 (MW)	20:80
3	$[PdCl_2(PPh_3)_2]$	K_3PO_4	Dioxane	100	35:65
4	$[PdCl_2(PPh_3)_2]$	K_2CO_3	THF	70	37:63
5	$[PdCl_2(PPh_3)_2]$	Et_3N	THF	70	35:65
6	$[Pd(PPh_3)_4]$	K_3PO_4	THF	70	85:15
7	$[Pd(PPh_3)_4]$	Cs_2CO_3	THF	70	90:10
8	$[Pd(PPh_3)_4]$	K_3PO_4	Dioxane	100	90:10
9	$[Pd(PPh_3)_4]$	K_3PO_4	Dioxane	100	>95:5[c]

[a] 5-Iodo-1,2,3-triazole **4c** (1 equiv), $PhB(OH)_2$ (2 equiv). [b] Determined by ^1H NMR spectroscopic analysis. [c] Reaction performed in a Schlenk tube.

observed (Table 4, entries 1–2). Activation under microwave irradiation did not improve the results (Table 4, entry 2), however phosphate and carbonate salts (entries 3–9) had a beneficial influence. The main parameter influencing the cross-coupling reaction was the use of $[Pd(PPh_3)_4]$ (Table 4, entries 6–9). The amount of 5-proto-triazole **3c** was significantly reduced and the desired 5-phenyl 1,2,3-triazole **17c** became the major isolated compound. The best solvent was dioxane and the use of a Schlenk tube provided more inert conditions (Table 4, entry 9), leading to the desired product **17c** with excellent selectivity and in high yield with only a trace amount of reduced triazole (>95:5).

The Suzuki cross-coupling with phenylboronic acid was then performed with 5-iodo- or 5-bromo-1,2,3-triazoles **4a–c** and **5c**, respectively (Scheme 6 and Table 5). The 5-bromo-triazole **5c** provided similar results in terms of yield to those of its iodinated counterpart **4c** (Table 5, entry 4). Deacetylation afforded 5-halogeno-1,2,3-triazoles **18a–c** as potential GP inhibitors.

Table 5. Synthesis of 5-aryl 1,2,3-triazoles **17** through Suzuki coupling.[a]

Entry	Starting material	R	X	Product	Yield [%][b]
1	**4c**	Ph	I	**17c**	95
2	**4a**	CH_2OAc	I	**17a**	96
3	**4b**	6-OMe-2-naphthyl	I	**17b**	94
4	**5c**	Ph	Br	**17c**	89

[a] Reaction conditions: **4a–c**/**5c** (1 equiv), $PhB(OH)_2$ (2 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), K_3PO_4 (2 equiv). [b] The value indicated is the isolated yield of 5-phenyl triazoles **17a–c** and the remaining material was composed of 5-proto triazoles **5**.

Attempted coupling of 5-iodo-1,2,3-triazole 4a to methyl acrylate through Pd-catalyzed Heck reaction

Compound **4a** and methyl acrylate were selected as partners for the Heck reaction. Assays carried out upon heating (120 °C, DMF) with $[Pd(PPh_3)_4]$ or $[Pd_2dba_3]$ (dba = dibenzylideneacetone) as catalysts and different bases (K_3PO_4, $NaHCO_3$, Cs_2CO_3) did not afford any coupled product but, instead, **3a** was isolated in high yield. Whereas previous coupling experiments did not yield any metallic intermediate, under the Heck conditions and after workup and column chromatography, a palladium-containing species **19**, similar to **I** (Scheme 4), was obtained (ca. 10% yield) and analyzed by ^1H NMR and MS. The ^1H NMR spectrum ($CDCl_3$) of **19** showed some striking features: a) A notable deshielding of H-2 (ca. 6.25 ppm) and H-1 (ca. 6.1 ppm) with shielding of H-3 (ca. 5.0 ppm) and of H-5 and H-6a (ca. 3.6 ppm); b) A spectacular shielding of H-6b (ca. 2.2 ppm), and of two acetoxy groups (ca. 1.6 and 1.2 ppm). The calculated isotopic distribution matched nicely the measured MS spectrum (see the Supporting Information). This is additional evidence for the existence of metal-associated triazole species, which are postulated to be involved in these types of reaction.

The synthetic methodologies afforded 1-glucosyl 4-substituted 5-bromo- and 5-iodo-1,2,3-triazoles in good yields; the same reaction performed with CuCl represents the first efficient atropodiastereoselective homocoupling, yielding unprecedented sugar-derived bis-triazole atropisomers. Subsequent Pd-catalyzed cross-couplings applied to 5-bromo- and 5-iodo-1,2,3-triazoles under Sonogashira or Suzuki conditions afforded a series of 1,4,5-trisubstituted triazoles. Deacetylation of these new molecules provided 23 potential inhibitors of GP.

Evaluation of GP inhibition

The synthesized products were tested as GP inhibitors. It is worth noting that glucosyl aryls and glucosyl heterocycles have also been identified as promising inhibitors of two additional targets that tightly control glycemia in humans. One is protein tyrosine phosphatases 1B (PTP1B), which inactivates the insulin receptor by dephosphorylation. When phosphorylated, this receptor is the starting point for insulin signaling through a cascade of events that is believed to be often impaired in diabetic patients. Therefore, provided that good levels of selectivity among the various existing phosphatases are achieved,[62] inhibitors of PTP1B, sometimes readily prepared through CuAAC, appear to have pharmacological potential as antidiabetic drugs.[63–65] A second approach targets the renal glucose transporters and, in particular, the sodium glucose cotransporter 2 (SGLT2), the inhibition of which can lead to excretion of plasma glucose into urine and reduced blood

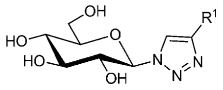
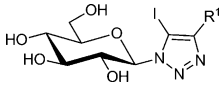
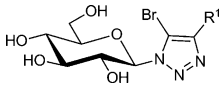
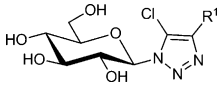
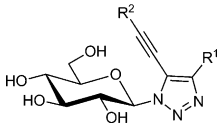
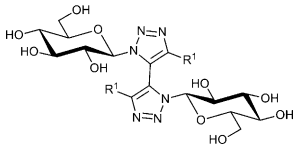
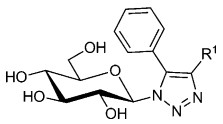
glucose levels in type II diabetic patients.[20] A series of 1-substituted 4-*C*-β-D-glucopyranosyl-1,2,3-triazoles was found to increase urinary glucose excretion in rats.[66]

The potential of each 1-glucosyl-1,2,3-triazole to inhibit RMGP*b* was evaluated in the direction of glycogen synthesis (Table 6). The introduction of three additional aromatic moieties (Table 6, entries 2, 4, and 5) did not provide better inhibitors than observed in earlier reports[32,33] (Table 6, entries 1 and 3). The introduction of a halogen atom at the 5-position of the triazole ring did not improve the inhibition towards GP (Table 6, entries 6–14). In particular, 5-iodinated derivatives **7** (Table 6, entries 6–10) displayed poorer inhibition than their 5-proto-1,2,3-triazole counterparts **6** (Table 6, entries 1–5). Similarly, 5-brominated derivatives **8** (Table 6, entries 11 and 12) did not display improved inhibitory potencies, nor did the 5-chlorinated compound **12a** (Table 6, entry 13). Apparently, the bulky substituents introduced did not fit into the catalytic site of the enzyme, resulting in weaker inhibitory potencies than the 5-proto-1,2,3-triazoles.

The influence of the substituent at the 5-position of the triazole ring was then studied with alkyne and phenyl moieties. From the family of nine 5-alkynylated-1,2,3-triazoles prepared, only two compounds bearing the hydroxymethyl and 6-methoxy-2-naphthyl[32,33] substituents either at the 4- or 5-positions (namely **16ab** and **16ba**) displayed interesting micromolar IC_{50} values (Table 6, entries 16 and 19). All other compounds were very poor inhibitors, thus supporting the conclusion that the 5-alkynyl and 5-phenyl moieties are probably not accommodated in the catalytic site of the enzyme. The activity of 5,5′-bis-triazole **14c** was also evaluated but this compound displayed very poor inhibition (Table 6, entry 25). Hence, the glucose-substituted triazoles reported herein showed only modest inhibitions of GP, indicating weak binding to the enzyme and, in particular, to its catalytic site.

Table 6. Inhibitory potency of substituted triazoles against RMGP*b*.

R^1
a CH_2OAc
b 6-OMe-2-naphthyl
c Ph
d *p*-MeOPh
e *p*-O_2NPh

Entry	Structure	Compound	IC_{50} [μM]
1		**6a**	26[a]
2		**6b**	31% @ 100 μM
3		**6c**	162[a]
4		**6d**	205.9 ± 2.2
5		**6e**	21% @ 200 μM
6		**7a**	714 ± 16
7		**7b**	103 ± 4
8		**7c**	849 ± 68
9		**7d**	50% @ 1 mM
10		**7e**	833 ± 35
11		**8a**	> 1000
12		**8b**	1038 ± 56
13		**12a**	476 ± 15
14		**12c**	not assayed[b]
15		**13a**	16% @ 1 mM
16		**16ab**	231 ± 7
17		**16ac**	16% @ 1 mM
18		**16ag**	32% @ 200 μM
19		**16ba**	190 ± 16
20		**16bb**	not assayed
21		**16bc**	4% @ 250 μM[c]
22		**16bg**	38% @ 200 μM
23		**13c**	not assayed
24		**14a**	not assayed[d]
25		**14c**	797 ± 8
26		**18a**	26% @ 500 μM
27		**18b**	812 ± 37[e]
28		**18c**	25% @1000

[a] Data previously reported by Somsak et al.[32,33] [b] The 5-chlorinated triazole **9c** could not be separated from its 5-proto-triazole analogue **6c** and therefore compound **12c** could not be obtained pure from **9c** for the inhibition measurements. [c] Inhibition could not be tested at higher concentrations due to poor solubility in water; solubilization required 20% DMSO. [d] Two conformers were identified by ^{13}C NMR spectroscopic analysis and therefore the mixture was not assayed. [e] Inhibition probably underestimated because centrifugation was required to remove insoluble material in water.

Conclusion

Atropisomerism is a characteristic feature of a number of natural and industrial products. A recent report[46] stated that "production of optically active 5,5′-bis-triazoles is expected to be of most interest for the synthesis of new chiral ligands and auxiliaries. In such compounds the heterocyclic core is a stereoelectronic and patentable modification of chiral biaryl cores, which are frequently encountered in ligands." To the best of our knowledge, we have disclosed[22] the first simple and practical atropodiastereoselective access to carbohydrate-derived bis-triazoles (> 55% yield). Their axial chirality was unambiguously established by X-ray diffraction analyses. It is notable that the use of a twofold excess of CuBr or CuI allowed the efficient introduction of Br and I halogen atoms at the 5-position (> 70% yield), and further Pd-catalyzed couplings with alkynes (Sonogashira) and phenylboronic acid (Suzuki) afforded a series of 5-substituted derivatives in good yields. The present study therefore provides general access to a variety of 1,4,5-trisubstituted 1,2,3-triazoles. This synthesis of atropisomeric bis-

triazoles required very simple chemistry derived from CuAAC and, in association with other studies, should pave the way for further developments.

Enzyme kinetic assays were performed for 26 O-unprotected 1-glucosyl-4,5-disubstituted 1,2,3-triazoles to study their inhibitory properties against RMGP*b*. The influence of the substituent at the 5-position of the triazole ring (either halogen, alkynyl or phenyl group) was detrimental, leading to the conclusion that the chemical space available in the catalytic site of the enzyme is not suited in terms of size and orientation to accommodate functional groups. The synthesized molecules did not reveal affinity for other GP binding sites.

Experimental Section

Kinetic experiements: RMGP*b* was isolated from rabbit skeletal muscle as described previously by using 2-mercaptoethanol.[67] Kinetic experiments were conducted in the direction of glycogen synthesis at 30 °C in the presence of 2 mM glucose-1-phosphate, 1 mM AMP and different inhibitor concentrations varying from 5 μM to 1 mM. Phosphate release was calculated according to reported methods.[68,69]

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Keywords: atropisomerism · carbohydrates · cycloaddition · cross-coupling · click chemistry

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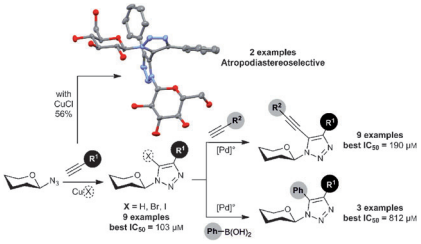
FULL PAPER

Halide decides: The use excess Cu^{I}-halide (X = Br, I) in azide–alkyne cycloadditions leads to predominant formation of 5-halogeno-1,2,3-triazoles (see scheme). In contrast, with CuCl, the major products exhibit two 5,5′-linked triazole rings and represent an efficient and highly atropodiastereoselective access to glucose-based 5,5′-bis-triazoles. Subsequent Pd-catalyzed Sonogashira and Suzuki couplings afforded 5-alkynylated and 5-phenyl derivatives in good yield. The products moderately inhibit glycogen phosphorylase.



Atropisomerism

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Efficient Atropodiastereoselective Access to 5,5′-Bis-1,2,3-triazoles: Studies on 1-Glucosylated 5-Halogeno 1,2,3-Triazoles and Their 5-Substituted Derivatives as Glycogen Phosphorylase Inhibitors