SHORT COMMUNICATION

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Intramolecular Glycosidation by Click Reaction Mediated Spacer Generation Followed by Spacer Cleavage

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Dedicated to Professor Yashwant D. Vankar on the occasion of his 60th birthday

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2-*O*-Propargyl-substituted glycosyl donors and *O*-(2-azidobenzyl)-substituted acceptors having a vicinal hydroxy group readily underwent the click reaction. Intramolecular glycosidation with *N*-iodosuccinimide/trifluoromethansulfonic acid as the activating system afforded β-(1–3)- and α-(1–2)-linked disaccharides as part of 14-membered macrocycles. Descriptors for these reactions are proposed that consider the donor and acceptor attachment sites and the stereochemistry of the functional groups. Investigation of the influence of 2-*O*-linked 1-aryl-1,2,3-triazol-4-ylmethyl groups, as contained in the spacer, on the anomeric selectivity exhibited no anchimeric assistance. In addition, it was shown that the spacer group can be readily cleaved under Birch reduction conditions.

Introduction

The rigid spacer concept for intramolecular glycoside bond formation consisting of (i) rigid spacer attachment to the glycosyl donor, (ii) regioselective attachment of the donor–spacer adduct to the acceptor, (iii) glycosidation, and (iv) cleavage of the spacer (and concomitantly the carbohydrate protecting groups) has led to excellent results regarding yield and anomeric selectivity, for instance, with *m*-xylylene spacers.[1,2] The results could be rationalized based on linkage- and configuration-dependent conformational preferences. Generally, attachment of the spacer to functional groups on the carbohydrate residues, which allows the formation of a 14-membered transition state in the glycoside bond-forming reaction and thus leads to a 14-membered glycoside bond containing a macrocycle, is favorable in the glycosidation step. However, the ligation of the glycosyl donor and acceptor with the *m*-xylylene spacer by using α,α′-dibromo-*m*-xylene as the alkylating agent is often a major hurdle, as in this linear approach to the product, the regioselective attachment of the donor–spacer adduct to the acceptor (step ii) does not always give good yields. Therefore, we recently turned our attention to the 1,2,3-triazole-forming click reaction[3,4] as a decisive ligation step between the glycosyl donor and acceptor.[5] Thus, a 2-*O*-propargyl-substituted glycosyl donor and an *O*-(*o*-azidomethyl)benzyl-substituted acceptor were separately prepared and then ligated in high-yielding click reactions. Basically, this more convergent strategy facilitates the generation of the starting materials for the intramolecular glycoside bond-formation reaction. However, as a result of rotational freedom between the triazolyl and benzyl residues, and accessible ring sizes of only 15-membered rings and higher, glycosidation yields and anomeric selectivities are not always satisfactory. In addition, cleavage of the *O*-(1-benzyl-1,2,3-triazol-4-yl)methyl group can be difficult.

To overcome the problems of the previous approaches, we investigated the *o*-azidobenzyl (OAB) group to generate the spacer (Scheme 1). This group, *O*-linked in the vicinal position to the accepting hydroxy group, can be regioselectively attached (step 1), offers the desired convenient linkage between the glycosyl donor and acceptor through a 1-aryl-1,2,3-triazole spacer (step 2), exhibits lower conformational mobility than the 2-azidomethylbenzyl group because of restricted conformational mobility and direct interaction between the triazolyl and phenyl moieties, and most importantly, permits the formation of a 14-membered ring in the glycosidation step (step 3) and favors convenient deprotection (step 4).

A precondition for these promising intramolecular glycosidation studies is the investigation of eventual anchimeric assistance through the attack of the nitrogen in the 3-position of the 1,2,3-triazolyl moiety at the anomeric carbenium ion generated in the glycosidation step (Scheme 2). Hence, the anomeric stereocontrol could be

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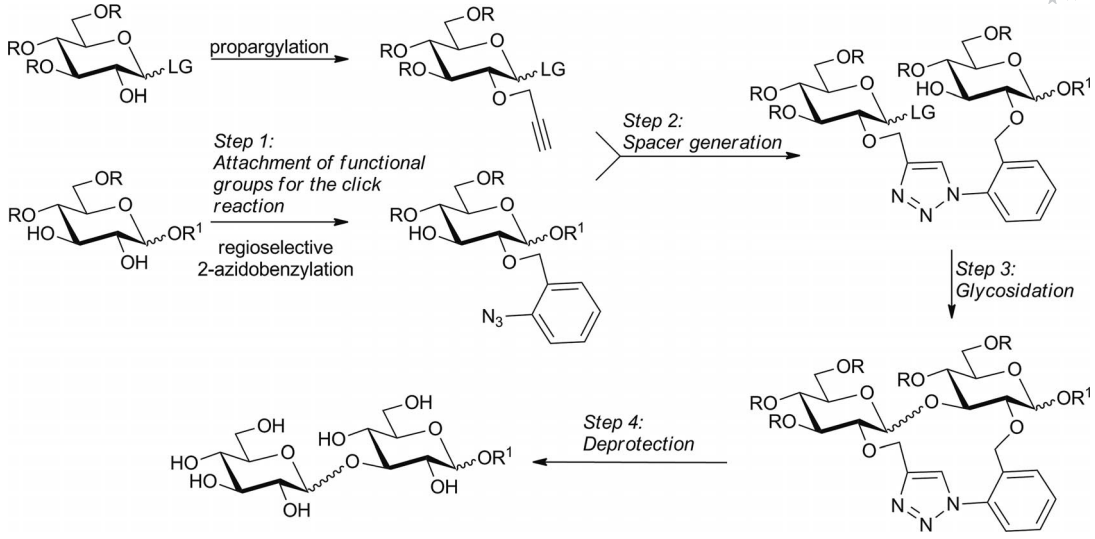
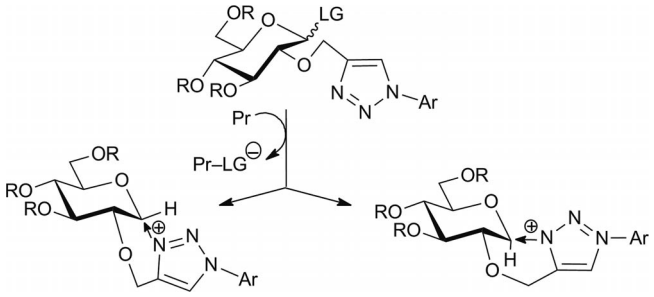


Scheme 1. Intramolecular glycosidation by click reaction mediated spacer generation.

strongly influenced by the 2-*O*-(1-aryl-1,2,3-triazol-4-yl)-methyl moiety; thus, selective access to both α- and β-glycosides governed mainly by the relative stereochemistry of the spacer attachment sites and the ring size in the glycosidation step could be limited. In addition, cleavage of the 2-*O*-(1-aryl-1,2,3-triazol-4-yl)methyl group to liberate the carbohydrate hydroxy groups (Scheme 1, step 4) is a further precondition for the investigation of this approach to intramolecular glycosidation.



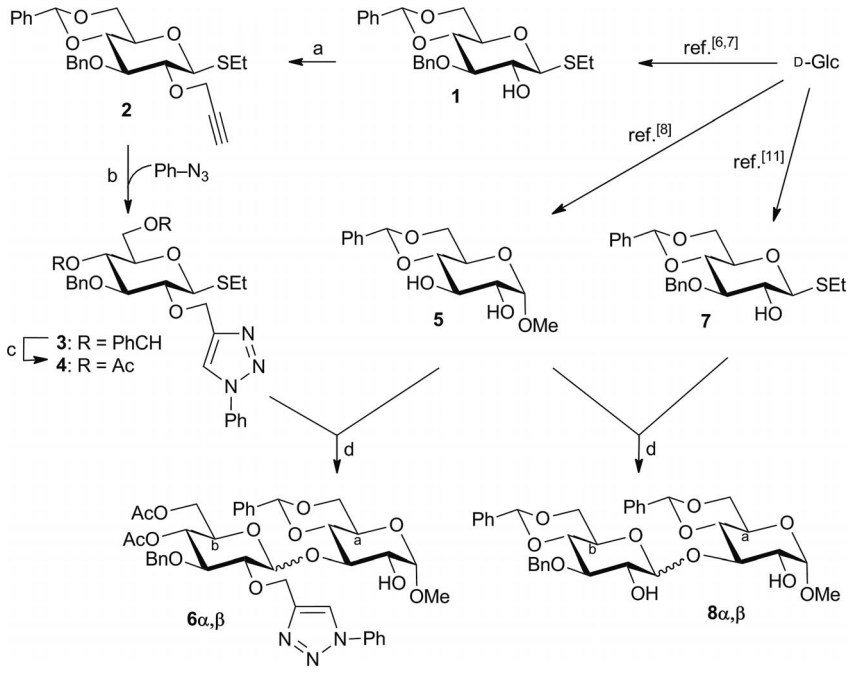
Scheme 2. Possible anchimeric assistance of a 2-*O*-(1-aryl-1,2,3-triazol-4-yl)methyl group in glycosidation reactions. LG = leaving group; Pr = promoter.

Results and Discussion

For the investigation of potential anchimeric assistance of the 2-*O*-(1-aryl-1,2,3-triazol-4-yl)methyl group in glycosidation reactions, ethyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-propargyl-1-thio-β-D-glucopyranoside (**2**) was prepared from known ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[6] that gave selectively, upon treatment with dibutyltin oxide (Bu_2SnO) in methanol and benzylation in the presence of cesium fluoride (CsF), 3-*O*-benzyl-protected derivative **1**[7] (Scheme 3). Reaction with propargyl bromide in the presence of sodium hydride as base afforded compound **2**. Reaction with phenylazide in the presence of Hünig's base (DIPEA; *N*,*N*-diisopropylethylamine) and CuI as catalyst[3,4] led to 2-*O*-(1-phenyl-1,2,3-triazol-4-yl)methyl-protected compound **3**. Selective acid-catalyzed debenzylidenation and immediate *O*-acetylation afforded glycosyl donor **4**. Glycosylation of 3-*O*-unprotected acceptor **5**[8] with an excess amount of *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoromethanesulfonic acid (TfOH)[9,10] at –40 °C to room temperature afforded a ca. 1:1 mixture of anomers **6α/6β** in good yield. Replacement of the 2-*O*-(1-phenyl-1,2,3-triazol-4-yl)methyl group by the nonparticipating benzyl group, as in known glucosyl donor **7**,[11] furnished, with **5** as the acceptor under the same conditions, a 1.2:1 mixture of anomers **8α/8β**[12] in high yield that could be separated. Hence, the 2-*O*-linked (1-phenyl-1,2,3-triazol-4-yl)methyl group exerts practically no anchimeric assistance in these glycosidation reactions,[13] though, as shown in Scheme 2, participation of N-3 in the stabilization of the anomeric carbenium ion via six-membered ring formation could take place from the α- and/or the β-side. Hence, the electron-donating character of the 1,2,3-triazolyl group seems to be rather low.[13]

The structural assignments and the anomeric ratios of disaccharides **6α**,**β** and **8α**,**β** were readily obtained from their NMR spectroscopic data. HSQC spectra furnished the shifts of anomeric C-1b and 1b-H and the 1b-H/2b-H coupling constants (Table 1) that support the structural assignments. The anomeric ratios were obtained from the integration of the signal of the anomeric *O*-methyl groups at C-1a.

To investigate the cleavage of an *O*-linked (1-aryl-1,2,3-triazol-4-yl)methyl group, known 6-*O*-unprotected glucopyranoside **9**[14] was treated with propargyl bromide under standard conditions to afford **10**;[15] with phenyl azide in the presence of Hünig's base and CuI, compound **10** gave 6-*O*-(1-phenyl-1,2,3-triazol-4-yl)methyl-substituted **11** (Scheme 4). Hydrogenation of this compound with Pd/C as catalyst in ethanol as solvent in the presence of trifluoroacetic acid (CF_3CO_2H) under different pressures (1, 8 atm) or with Rh/C as catalyst led to *O*-debenzylation to afford,

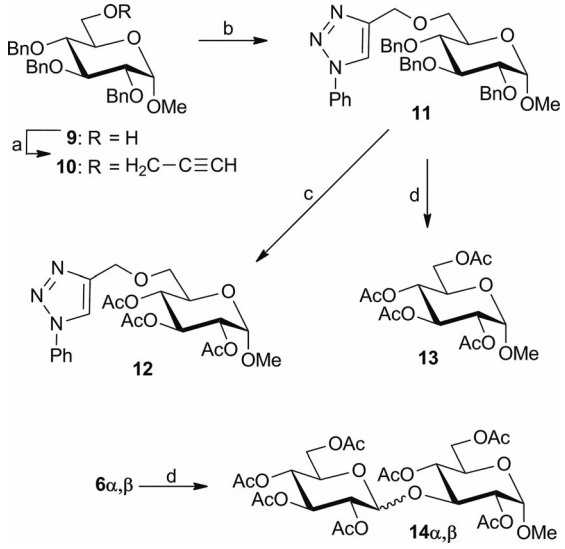


Scheme 3. Investigation of anchimeric assistance of the (1,2,3-triazol-4-yl)methyl group. Reagents and conditions: (a) Propargyl bromide, NaH, DMF, 0 °C (86%); (b) CuI, DIPEA, CH_2Cl_2 (81%); (c) *p*TsOH, CH_2Cl_2/MeOH (1:1), r.t.; Ac_2O, Pyr (98%); (d) NIS, TfOH, CH_2Cl_2, –40 °C (**6α**,**β**: 73%, α/β ≈ 1:1; **8α**,**β**: 86%, α/β ≈ 1.2:1).

Table 1. ^1H (1b-H) and ^{13}C (C-1b) NMR chemical shift assignments of compounds **6α**,**β** and **8α**,**β**.[a]

Compound	C-1b shift [ppm]	1b-H shift [ppm]	$^3J_{1b,2b}$ [Hz]
6α	95.6	5.62	3.6
6β	102.9	4.86	6.4
8α	97.1	5.48	4.0
8β	102.4	5.04	6.8

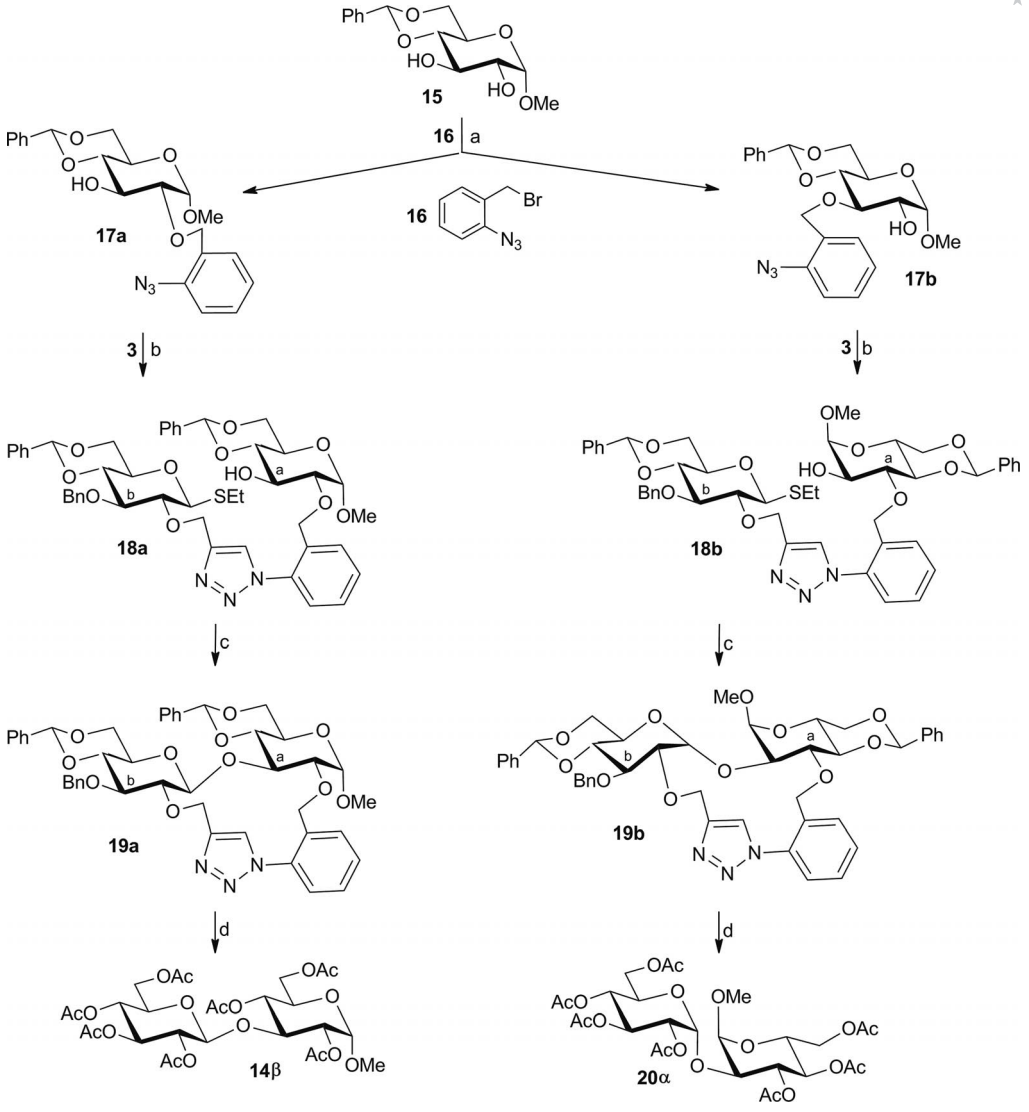
[a] ^1H (600.3 MHz) and ^{13}C (90.6 MHz) NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard. For the complete ^1H and ^{13}C NMR spectroscopic data, see the Supporting Information.



Scheme 4. Deprotection of *O*-(1-phenyl-1,2,3-triazol-4-yl)methyl-substituted compounds. Reagents and conditions: (a) see ref.[15]: HC≡C–CH_2Br, NaH, DMF, 0 °C (84%); (b) CuI, DIPEA, CH_2Cl_2, r.t. (76%); (c) Pd/C, H_2, CF_3CO_2H, EtOH, 1 atm; Ac_2O, Pyr (81%); at 8 atm (76%); with Rh/C as cat. (74%); (d) liq. NH_3, Na, –78 °C; Ac_2O, Pyr (**13**: 72%; **14**: 63%).

after *O*-acetylation, product **12**; if at all, only very minor cleavage of the (1-aryl-1,2,3-triazol-4-yl)methyl group took place. Therefore, Birch reduction conditions were applied to compound **11**, which led to full deprotection as shown with known, fully *O*-acetylated derivative **13**.[16] Hence, the products to be received in the intramolecular glycosidation should also be accessible by this deprotection procedure. As first proof, disaccharide **6α**,**β** was treated under Birch conditions to afford, after per-*O*-acetylation, desired and known disaccharide **14α**,**β**.[17] Therefore, omission of the methylene group, contained between N-1 of the triazolyl and the benzyl residue in the previously employed spacer,[5] is decisive for convenient cleavage of the *O*-linked (1,2,3-trizazol-4-yl)methyl group.

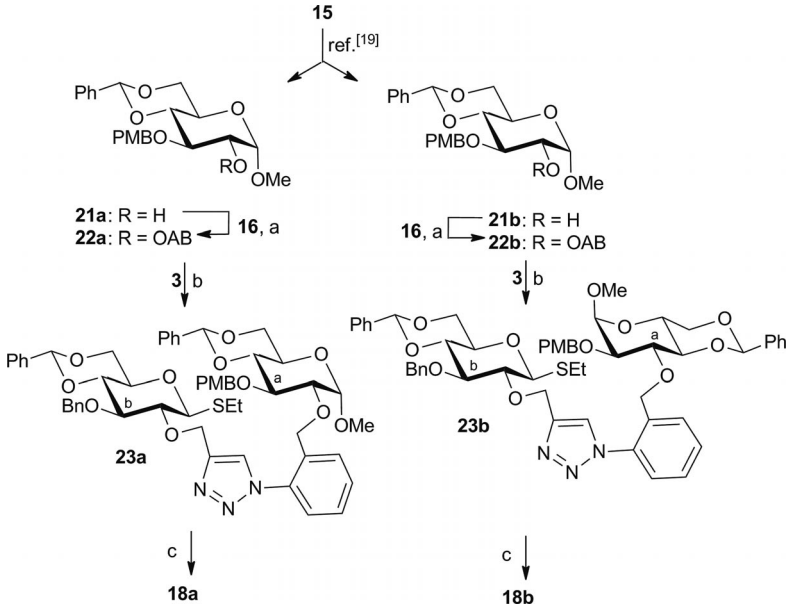
Synthesis of the acceptor for the intramolecular glycosidation studies started from 4,6-*O*-benzylidene-protected glucopyranoside **15** (Scheme 5). Treatment of **15** with *o*-azidobenzyl bromide (**16**)[18] in NaOH/dichloromethane in the presence of tetrabutylammonium iodide (TBAI) (to avoid high regioselectivity as obtained in the synthesis of **2**) afforded a 3:1 mixture of desired isomers **17a**/**17b** that could be readily separated. Standard click reaction with glycosyl donor **3** furnished desired donor–spacer–acceptor intermediates **18a** and **18b**, respectively, in high yield. Their structures were independently confirmed by transforming **15** into known *p*-methoxybenzyl (PMB)-protected derivatives



Scheme 5. Intramolecular glycosidation with donor–spacer–acceptor-linked intermediates **18a** and **18b**. Reagents and conditions: (a) NaOH/CH_2Cl_2, TBAI, r.t. (**17a**: 48%; **17b**: 16%); (b) CuI, DIPEA, CH_2Cl_2, r.t. (**18a**: 78%; **18b**: 82%); (c) NIS, TfOH, CH_2Cl_2, –40 °C to r.t. (**19a**: 68%; β/α > 25:1; **19b**: 79%, α/β = 8:1); (d) liq. NH_3; Na, –78 °C; Ac_2O, Pyr (**14β**: 70%; **20α**: 72%).

21a and **21b**[19] (Scheme 6). Reaction of **21a** and **21b** with **16** in the presence of NaH as base and in DMF as solvent furnished **22a** and **22b**, respectively. Click reaction with **3** led to **23a** and **23b** that upon removal of the PMB group with DDQ in CH_2Cl_2/H_2O furnished starting materials **18a** and **18b** for the intramolecular glycosidation. Standard glycosidation conditions (NIS, TfOH) applied to **18a** led to the disaccharide moiety contained in 14-membered macrocycle **19a**; practically, only β(1–3)-linkage formation was observed. This could be confirmed by complete deprotection of **19a** under Birch reduction conditions and then *O*-acetylation with acetic anhydride in pyridine to afford known methyl laminaribioside **14β**[17] in 70% yield over the two steps. Hence, the anomeric selectivity difference between the intramolecular glycosidation (Scheme 5) and the related intermolecular variant of **4** with **5** shown in Scheme 3 is noteworthy.

For the description of intramolecular glycosidation reactions, the linkage of the spacer to the donor (position of spacer attachment and accepting hydroxy group and their relative stereochemistry) was previously employed.[1a] Thus, for the reaction of **18a**, the descriptor is 2b-*O*(α)/(2a→3a)-*O*-L-*threo* glycosidation. Isomer **18b** also possesses a 2b-*O*(α)/(3a→2a)-*O*-L-*threo* connection between the donor and acceptor. Hence, as the ring size and the spacer are the same as those in **18a**, the same glycosidation result, that is, β(1–2)-linkage in the product, was expected. However, under standard glycosidation conditions from **18b**, mainly α-(1–2)-linked product **19b** was obtained, as was confirmed after deprotection under Birch reduction conditions and then *O*-acetylation to afford methyl kojibioside **20α**[20] in 72% yield over the two steps. A more careful look at the accepting hydroxy groups in **18a** and **18b** reveals that the stereochemistry of the functional groups vicinal to the accepting hy-



Scheme 6. Alternative synthesis of compounds **18a** and **18b**. Reagents and conditions: (a) NaH, DMF, 0 °C to r.t. (**22a**: 88%; **22b**: 84%); (b) CuI, DIPEA, CH_2Cl_2, r.t. (**23a**: 89%; **23b**: 85%); (c) DDQ, CH_2Cl_2/H_2O, 0 °C (**18a**: 76%; **18b**: 79%).

droxy groups also has to be considered and included in the description of intramolecular glycosidations. Thus, for **18a** a 2b-*O*(α)/(2a→4a)-*O*-L-*xylo* and for **18b** a 2b-*O*(α)/(3a→1a)-*O*-L-*lyxo* descriptor is assigned. Obviously, the accepting hydroxy group in **18b** is comparable to the 3-hydroxy groups in galactopyranosides that, as a result of the accumulation of lone pair orbitals on the β-side, exhibit increased nucleophilicity. In **18b**, this effect is gained when the donor moiety approaches with its α-side.

The practical validity of this proposal for the description of intramolecular glycosidations has to be displayed by further studies. It is hoped that with this readily accessible spacer between *O*-benzyl- and/or *O*-benzylidene-protected donors and acceptors data for the α/β-selectivities of intramolecular glycosidations may finally become available, which would permit reliable planning of the required building blocks for stereoselective glycosidation reactions. As the number of different combinations between D-gluco-, D-galacto-, and D-mannoypranoses and their 2-amino-2-deoxy derivatives is quite limited, this task is within experimental reach.

Conclusions

In conclusion, spacer generation from 2-*O*-propargyl-substituted glycosyl donors and *O*-(2-azidobenzyl)-substituted acceptors through the 1,2,3-triazole-forming click reaction leads readily to donor–spacer–acceptor constructs for the study of intramolecular glycosidation reactions. In the glycosidation step, the formation of the 14-membered macrocycle proceeded with high anomeric selectivity. Anchimeric assistance by the triazolyl group was not observed. The reactions are described by considering the attachment sites and the stereochemistry of the donor and the acceptor. Besides the ring size, the relative orientation of the spacer attachment site, the accepting hydroxy group, and the vicinal functional groups seem to be of particular importance for the anomeric selectivity. On the basis of these descriptors of the donor–spacer–acceptor constructs, the chemical and stereochemical results of glycosidation reactions should become predictable. Thus, the design of a reliable building block for programmable oligosaccharide syntheses should become available.

Supporting Information (see footnote on the first page of this article): Experimental details and ^1H and ^{13}C NMR spectra of new compounds (**2, 3**, **4**, **6α,β**, **8α**, **8β**, **11**–**14α,β**, **17a**–**19a**, **14β**, **17b**–**19β**, **20β**, **22a**, **23a**, **18a**, **21b**–**23b**, **18β**) and ^1H NMR spectra of known compounds (**1**, **5**, **7**, **9**, **10**, **15**, **16**).

Acknowledgments

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