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En Route to Novel Furanoside Mimics through Stereoselective Zinc-Mediated Propargylation of *N*-Benzyl Glycofuranosylamines Using Ultrasound Activation

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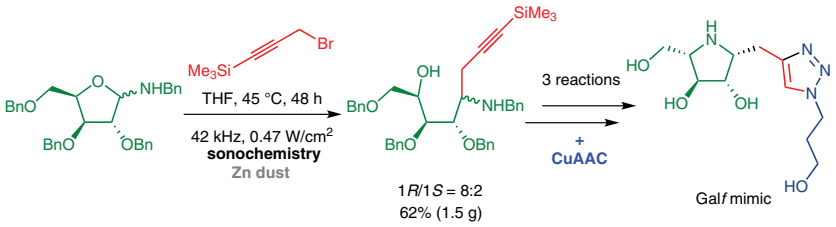

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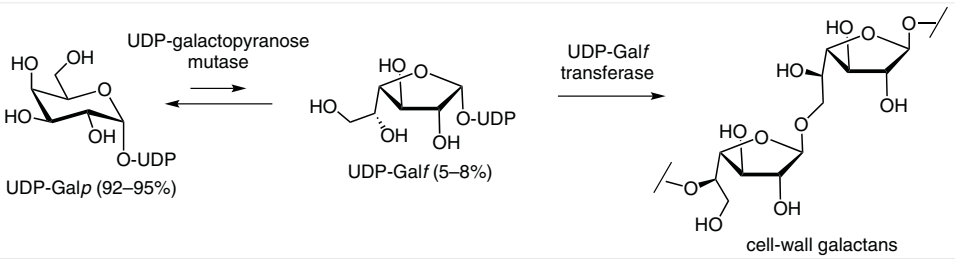
Abstract Preliminary results on a novel zinc-mediated, ultrasound-promoted chain extension of glycofuranosylamines with a propargyl group are reported. The procedure was applied to D-*arabino* and D-*xylo* substrates to give, via Cram-chelate transition states, 1-*C*-1-(3-trimethylsilyl-2-propynyl)-1-benzylamino pentionols in moderate to good yields and acceptable stereoselectivities (*syn*/*anti* ≥4:1). To apply the reaction to the synthesis of galactofuranoside mimics, the D-*xylo* intermediate was cyclized to afford a 1-*C*-1-(2-propynyl)-1,4-dideoxy-1,4-imino-L-arabinitol derivative in excellent yield. This building block was used in three examples of CuAAC click reactions with azide compounds to provide the corresponding galactofuranoside mimics.

Key words propargylation, *N*-benzyl glycofuranosylamines, stereoselective synthesis, iminosugars, Huisgen cycloaddition, furanoside mimics

Carbohydrates are involved in numerous key biological processes such as signal transduction, recognition by the immune system, glycolysis and gluconeogenesis.[1] Carbohydrate-processing enzymes such as glycosidases and glycosyl transferases are increasingly important targets in medicinal chemistry, and their inhibitors can be used in therapies directed at cancer, viral infections, lysosomal storage diseases, diabetes, etc.[2–4] In this context, the six-membered ring form of sugars has so far attracted most attention in the design of carbohydrate mimics. Nonetheless, as a result of the increasing demand for original therapeutic agents, emerging multidrug resistance and the improved knowledge of bacterial cell glycoconjugates, furanoses and furanosides are becoming increasingly important structural elements. Indeed, carbohydrates in the thermodynamically less favorable furanose form are absent in mammalian glycoconjugates, but are widespread in the glycans produced by many algae, lichen and marine sponges and, more importantly, in several fungi, protozoa and bacterial pathogens.[5] In bacteria, these furanosides are often found in cell-surface glycans and are essential for viability, virulence and/or integrity of the organisms. Thus it becomes evident that enzymes promoting the biosynthesis/biodegradation of bacterial furanosides are of general interest as targets to produce novel selective antimicrobial chemotherapeutics.

For instance, the major structural component of the *Mycobacterium tuberculosis* cell wall, known as the mAGP complex, contains a galactan chain of approximately 35 D-galactofuranose (D-Gal*f*) units,[6] and its biosynthesis is essential for viability of the mycobacterium.[7] Typically, UDP-Gal*f* biosynthesis occurs from uridine diphosphogalactopyranose (UDP-Gal*p*) by the action of UDP-Gal*p* Mutase (UGM), which promotes the ring contraction.[8] In the second step, UDP-Gal*f* is converted into a glycoside by the action of two galactofuranosyltransferases (e.g., Gal*f*T1 and Gal*f*T2) usually with inversion of configuration to form a β-glycoside (Scheme 1).[8,9] Recent elegant bioorganic experiments have underlined the fact that the two biochemical reactions occur by way of oxocarbenium-like transition states.[9,10]

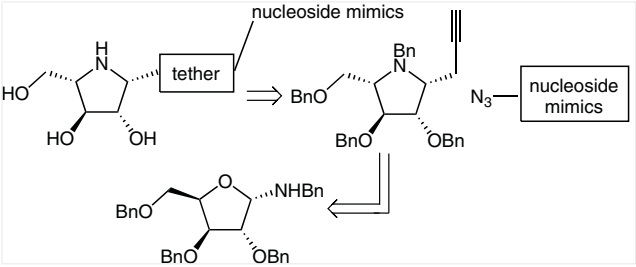


Scheme 1 UDP-galactofuranose and galactan biosynthesis

Since iminosugars constitute mimics of such positively charged transition state,[2,11] our group has focused on the synthesis of a diversity of 1,4-imino-D-galactitol carrying *C*-linked aglycones, designed to mimic UDP-Gal*f*, the substrate of both UGM and Gal*f*Ts.[12] Of note, the new compounds showed modest inhibitions of UGM but significant activities towards Gal*f*T2 were observed.[13]

However, the synthesis of 1,4-iminogalactitol derivatives required the rather tedious preparation of 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose,[12a,b,d,14] and we decided to continue to work in this area in the pentofuranose series, the L-arabinofuranose structure being equivalent in ring configuration to the D-Gal*f* structure. In addition, we sought a strategy that would allow the rapid tethering of a diversity of functional groups to the iminopentitol scaffold, in order to access a variety of UDP-Gal*f* mimics, as outlined in Scheme 2 (see below).

This could be achieved using a propargyl appendage on the iminopentitol moiety that could be used to connect various groups by azide-click chemistry or other cycloaddition processes. Thus, the synthesis of 1-*C*-(2-propynyl)iminopentitols became our first objective. To our knowledge, a single example of a 1-*C*-iminosugar featuring a terminal 2-propynyl group has been reported in the literature.[15] However, in this work by Compain et al., the propargyl group was generated from an allyl group. In our previous work, we have shown that the addition of propargyl-TMS in the presence of TMSOTf to *N*-CbZ glycosylamines predictably led to allenyl-substituted derivatives that were cyclized to 1-*C*-allenyl iminogalactitol derivatives.[12d] We therefore looked for a different methodology that would allow the direct introduction of the propargyl group by an addition to a glycosylamine, this sequence offering a very concise approach to 1-*C*-substituted iminosugar derivatives.[16] We report herein our preliminary results on a novel methodology to produce 1-*C*-propargyl iminopentitols in moderate yields and its application to prepare galactofuranoside mimics. The method involves the stereoselective addition of a propargylic zinc reagent onto *N*-benzyl glycofuranosylamines.



Scheme 2 Retrosynthetic strategy

Retrosynthetic analysis from L-*arabino* iminopentitols requires a D-xylofuranosylamine as the starting material, the addition of a metalated species, followed by a cyclization with inversion at C-4, to generate the desired L-*arabino* configuration (Scheme 2).

For initial investigations, and to determine the feasibility of our methodology, we first selected *N*-benzyl-2,3,5-tri-*O*-benzyl-α/β-L-arabinofuranosyl amine **1** as a standard substrate, this compound being more easily accessible than its D-*xylo* isomer, as it can be obtained from commercial 2,3,5-tri-*O*-benzyl-L-arabinofuranose **2** and an excess of benzylamine (2 equiv) in anhydrous CH_2Cl_2. The alkylation process was then investigated (Table 1).

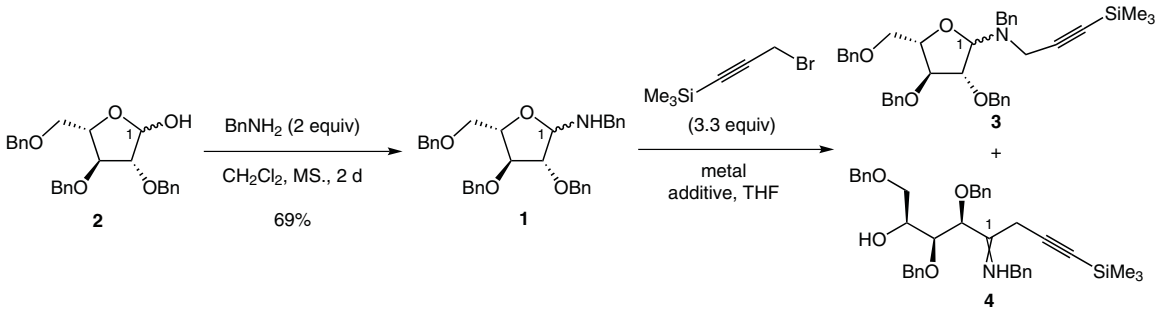
Overall, promoting the reaction by indium gave no propargylation at all.[17] Degradation was observed on heating from 20 °C to 60 °C and some N-propargylation of **1** gave compound **3** which was isolated in 7% yield (entry 1). Addition of propargyl Grignard reagent,[18] prepared using magnesium turnings under mercury-free catalysis ($ZnBr_2$ catalysis) was not successful either, with a mixture of debenzylated **1** and **4** being obtained (entry 2). Copper(I) reagents were also considered using Kobayashi conditions, but no reaction was detected (entry 3).[18]

Next, reactions with propargyl zinc were examined. Zinc reagents are known to be less basic than their Grignard and copper counterparts[19] and we considered that this might prevent debenzylation and/or elimination by-products. These reagents are also more reactive than indium-based reagents, but less so than copper and magnesium derivatives.[19] They have been shown to react with *N*-benzyl glycosylamines to give the corresponding adducts in reasonable yields.[20] However, in our case, no addition was observed when using zinc dust preactivated with iodine (entry 4), LiCl (entry 5) or dilute HCl (entry 6).[21] It should be noted that glycosylamines are somewhat sensitive to traces of acid. In the case of I_2 preactivation, **2** was observed among other degradation products. We assumed this to be due to the formation of Lewis acidic ZnI_2. Using Et_2Zn with Wilkinson catalyst or CuI to promote zinc insertion, yet again no propargylation was observed (entries 9 and 10).[21]

Ultrasound is an efficient and relatively innocuous means of activation in synthetic chemistry.[22] Recent reports, by Suslick in particular,[23] have highlighted the importance of ultrasound to promote generation of organometallic reagents and for the activation of zinc powder.

Sonication had a very beneficial effect on our system; when the reaction mixture was partly submerged in a standard ultrasound laboratory cleaner (0.47 W/cm^2, 42 KHz) at 40 °C, compound **4** was formed and then isolated in 48% yield with a 9:1 diastereoselectivity (entry 7). Interestingly similar yields (48% vs. 39%) and diastereoselectivities were observed when the reactions were carried out under Barbier conditions or by preforming the zinc reagent during two

Table 1 Optimization of the Propargylation Reaction

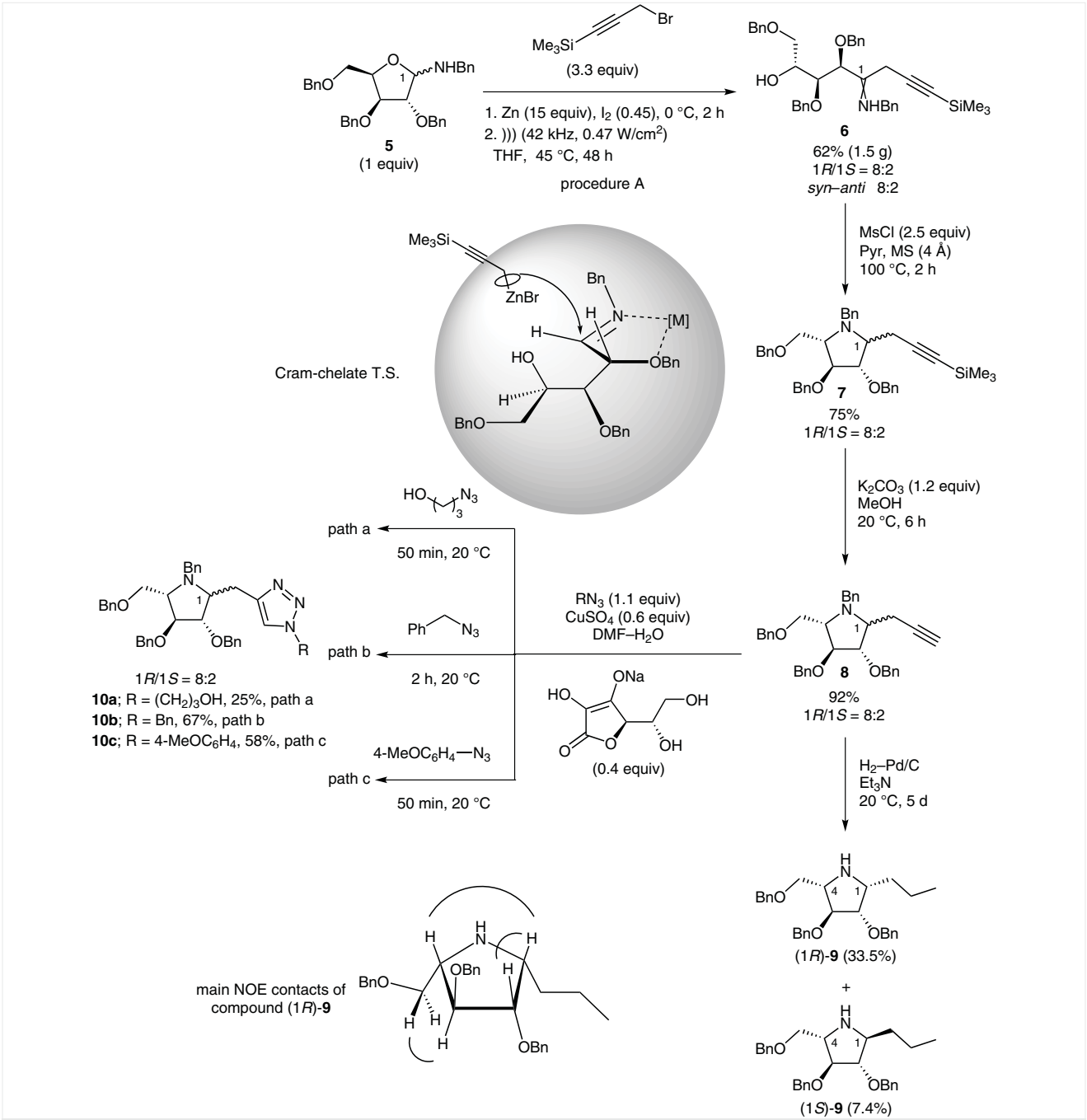


Entry	Metal (equiv)[a]	Additive (equiv)	Time (h)	Temp (°C)	Ratio *syn*/*anti*[b]	Yield (%)[c]	Observation
1	In (3.3)[d]	–	48	20–60	–	–	**1** <15% recovered **3** (7%) + degradation
2	Mg (6.6)	$ZnBr_2$ (0.2)	20	0–20	–	–	mixture of partially debenzylated **1** and **4**
3	CuCN (6.9)	$ZnBr_2$ (0.2) $MgCl_2$ (6.6)	20	0–20	–	–	no reaction
4	Zn (15)[d]	I_2 (0.45)	48	0–40	–	–	**1** (60%) + degradation + **2**
5	Zn (10)[d]	LiCl (10)	48	0–50	–	–	no reaction
6	Zn (HCl)[d,e] (10)	–	48	0–50	–	–	no reaction
7	Zn (15)	I_2 (0.45)	48	0–45,)))	9:1[f]	48	**4** + degradation (procedure A)
8	Zn (15)[d]	I_2 (0.45)	48	0–45,)))	9:1[e]	39	**4** + degradation (procedure B)
9	Et_2Zn (3.3)	$RhCl(PPh_3)_3$ (0.05)	72	0–50	–	–	no reaction
10	Et_2Zn (3.3)	CuI (0.05)	48	0–50	–	–	no reaction

[a] Reactions were carried out on 0.1–0.2 mmol scales of **1**.
[b] Diastereoselectivity was determined by ^1H NMR analysis.
[c] Isolated yield.
[d] Barbier conditions.
[e] Dilute aq HCl (0.1 M) was used for activation.
[f] We propose (*syn*)-**4** to be the major diastereomer by analogy with compound **6**.

hours at 0 °C [see procedure **A**[24] (entry 7) and procedure **B**[25] (entry 8), respectively]. We assumed the major diastereomer to be the (1*R*)-**4** epimer (the *syn* diastereomer) based on Cram-chelate control (see Supporting Information and Scheme 3).[26] To validate the method, we reacted *N*-benzyl-2,3,5-tri-*O*-benzyl-D-xylofuranosylamine (**5**) under the conditions of procedure **A**. To our satisfaction, compound **6** was obtained in 62% yield (1.5 g scale) with 4:1 diastereoselectivity.[27] Compound **6** was cyclized under the typical conditions (mesylation using mesyl chloride in pyridine at 100 °C) to give 1-*C*-(3-trimethylsilyl-2-propynyl)imino-L-arabinitol **7** in 75% yield. The trimethylsilyl protecting group was then removed (K_2CO_3 in MeOH, 20 °C) to afford imino-L-arabinitol **8** in 92% yield. No erosion of the diastereoselectivity was noticed. To determine the diastereoselectivity of the propargylation process, compound **8** was partly hydrogenolyzed (H_2, 2-propanol, Et_3N, 10% Pd–C, 20 °C) to provide (1*R*)-**9** and (1*S*)-**9** in a 4:1 ratio which were separated by silica chromatography (ethyl acetate–petroleum ether 7:3). Using ^1H NMR, ^{13}C NMR, correlation spectroscopy (COSY) and nuclear Overhauser effect spectroscopy (NOESY), compound (1*R*)-**9** (arising from *syn*-**6**) was established to be the major diastereomer (see Supporting Information). The Gal*f* derivatives were then synthesized by CuAAC click chemistry from the parent imino-L-arabinitol **8** and a set of azide derivatives (Scheme 3: 3-azidopropan-1-ol, path a; benzyl azide, path b; and 1-azido-4-methoxybenzene, path c). This small set of molecules was carefully chosen to ensure a relatively high degree of diversity for future potential Gal*f* mimics. The corresponding clicked derivatives **10a**–**10c** were obtained in low to good unoptimized yields (25%, 67% and 58% for **10a**–**c**, respectively). To finalize the synthetic strategy, compound (*R*)-**10a** was then submitted to hydrogenation for 24 hours at 20 °C

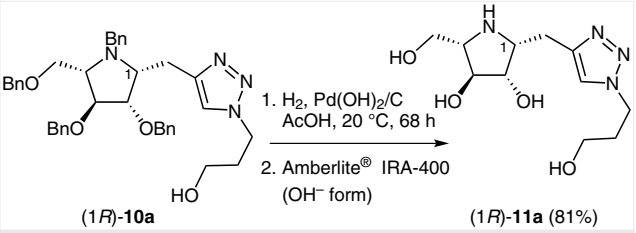
using standard conditions [H_2, 20% $Pd(OH)_2/C$ in AcOH]. Further $Pd(OH)_2/C$ was added and the reaction mixture was stirred for another 48 hours to afford (*R*)-**11a** as a model Gal*f* mimic based on an imino-α-L-arabinitol core, a triazolyl linker and a functionalized chain (vide infra, Equation 1).[28]



Scheme 3 Synthetic strategy to prepare original Gal*f* analogues using a novel zinc-mediated propargylation and postfunctionalization

In summary, we report herein preliminary results on a new, convenient method to generate quickly furanoside mimics based on 1-C-substituted iminopentitol scaffold. The methodology involves a novel, stereoselective zinc-mediated propargylation of *N*-benzyl glycofuranosylamines and uses ultrasounds as a critical mode of activation, followed by a mesylation, cyclization, cycloaddition and deprotection sequence. To illustrate this strategy, a 1-*C*-

1-(2-propynyl)-1,4-dideoxy-1,4-imino-L-arabinitol scaffold was thus prepared (1.5 g scale) and three galactofuranoside mimics were generated by CuAAC click chemistry.



Equation 1 Hydrogenolysis of (1*R*)-**10a** to prepare Gal*f* mimic (1*R*)-**11a**

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379551

Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0061th.

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(24) **Procedure A**: In a 10-mL round-bottom flask under an argon atmosphere were added zinc dust (96.2 mg, 1.47 mmol) and iodine (11.2 mg, 0.04 mmol). The flask was placed under vacuum and the vessel was heated with a heat gun during 5 min. The vessel was filled with argon and allowed to reach r.t. The cycle was repeated once and anhyd THF (2 mL) was then added followed by 3-bromo-1-trimethylsilyl-1-propyne at 0 °C (53 µL, 0.32 mmol; mixture A). The reaction mixture was allowed to warm to r.t. and stirred for a further 2 h. In parallel, a solution of the *N*-benzyl-2,3,5-tri-*O*-benzyl-α/β-furanosylamine (0.10 mmol) in anhyd THF (2 mL) under argon was prepared in a 10-mL round-bottom flask (mixture B). Solution A was added to solution B via cannula, avoiding transferring too much zinc powder into solution B. The reaction mixture was stirred under ultrasonication for 48 h (45 °C, 42 kHz, 0.47 W/cm^2). The resulting mixture was then filtered through Celite® and the residue was washed with EtOAc. The organic phase was washed with H_2O, aq NH_4Cl, sat. aq $NaHCO_3$ and dried over $MgSO_4$. The organic phase was filtered and concentrated under vacuum. The residue was purified by column chromatography (silica gel, petroleum ether–EtOAc, 8:2) to give the corresponding propargylated pentitols as a mixture of two diastereomers.

(25) **Procedure B**: In a 10-mL round-bottom flask under an argon atmosphere were added zinc dust (96.2 mg, 1.47 mmol) and iodine (11.2 mg, 0.04 mmol). The flask was placed under vacuum and the vessel was heated with a heat gun during 5 min. The vessel was filled with argon and allowed to reach r.t. The cycle was repeated once and anhyd THF (4 mL) was then added followed by 3-bromo-1-trimethylsilyl-1-propyne (53 µL, 0.32 mmol) and the *N*-benzyl-2,3,5-tri-*O*-benzyl-α/β-furanosylamine (0.10 mmol) under argon atmosphere. The reaction mixture was stirred under ultrasonication for 48 h (45 °C, 42 kHz, 0.47 W/cm^2). The resulting mixture was then filtered through Celite® and washed with EtOAc. The organic phase was washed with H_2O, aq NH_4Cl, sat. aq $NaHCO_3$ and dried over $MgSO_4$. The organic phase was filtered and concentrated under vacuum. The residue was purified by column chromatography (silica gel, petroleum ether–EtOAc, 8:2) to give the corresponding propargylated pentitols as a mixture of two diastereomers.

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(27) Diastereomers of compound **6** could not be separated on regular silica gel column chromatography and were thus further processed as a mixture of isomers.

(28) **Spectroscopic Data for Selected Compounds**:
(1*R*)- and (1*S*)-1-*C*-(3-Trimethylsilyl-2-propynyl)-2,3,5-tri-*O*-benzyl-1-benzylamino-1-deoxy-D-xylitol [(1*R*)-6 and (*1S*)-6]: colorless oil; (1*R*)-**6** and (1*S*)-**6** were obtained as a 8:2 mixture of diastereomers; $[\alpha]_D^{20}$ −17.3° ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.19–7.36 (m, 20 H), 4.34–4.71 (m, 6 H), 4.12 (d, *J* = 6.5 Hz, 0.8 H), 4.08–4.11 (dd, *J* = 8.2, 5.8 Hz, 0.8 H), 4.00–4.06 (m, 0.2 H), 3.88 (d, *J* = 12.5 Hz, 0.2 H), 3.85 (d, *J* = 12.1 Hz, 0.8 H), 3.80–3.82 (m, 0.2 H), 3.78 (br d, *J* = 6.6 Hz, 0.8 H), 3.62–3.70 (m, 1 H), 3.48–3.62 (m, 2.2 H), 3.33 (dd, *J* = 9.4, 3.6 Hz, 0.8 H), 3.08 (dd, *J* = 12.0, 4.0 Hz, 0.2 H), 2.71–2.84 (m, 1 H), 2.63–2.70 (m, 0.2 H), 2.48 (dd, *J* = 16.7, 9.5 Hz, 0.8 H), 0.06–0.19 (m, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ = 139.1, 138.7, 138.6, 138.5, 138.4, 138.2, 138.1, 137.9, 127.5–128.8, 104.2, 103.7, 88.0, 87.5, 79.0, 78.9, 77.9, 75.3, 73.9, 73.7, 73.6, 73.2, 73.7, 73.2, 73.0, 71.1, 70.8, 68.0, 66.4, 57.3, 53.9, 50.6, 50.6, 22.5, 20.9, 0.1–0.5. IR (film): 3030, 2862, 2171, 1496, 1453, 1360, 1249, 1207, 1071, 1027, 907, 841, 726, 696, 645 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{48}NO_4Si$: 622.334712; found: 622.334699.
(1*R*)- and (1*S*)-1-*C*-(3-Trimethylsilyl-2-propynyl)-*N*-benzyl-2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-L-arabinitol (7): light yellow oil; 8:2 mixture of diastereomers (1*R*)-**7** and (1*S*)-**7**: $[\alpha]_D^{20}$ −14.5° ($CHCl_3$, *c* = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.14–7.39 (m, 20 H), 4.22–4.60 (m, 6 H), 4.06–4.12 (m, 0.4 H), 3.97 (d, *J* = 10.9 Hz, 0.8 H), 3.95 (br s, 0.8 H), 3.91–3.94 (m, 0.2 H), 3.88 (br s, 0.8 H), 3.76 (d, *J* = 13.9 Hz, 0.8 H), 3.71 (d, *J* = 14.6 Hz, 0.2 H), 3.53–3.58 (m, 0.4 H), 3.27–3.38 (m, 1.8 H), 3.20–3.26 (m, 0.2 H), 3.07–3.16 (m, 1.6 H), 2.56 (dd, *J* = 16.6, 9.3 Hz, 0.8 H), 2.44–2.59 (m, 0.2 H), 2.34 (br s, 0.2 H), 2.40 (dd, *J* = 16.6, 5.1 Hz, 0.8 H), 0.05–0.19 (m, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ = 139.6, 139.5, 138.7, 138.5, 125.4–129.2, 106.0, 105.2, 86.8, 86.3, 86.0, 85.4, 83.5, 82.7, 73.3, 73.0, 72.7, 71.7, 71.6, 71.0, 72.0, 70.6, 69.7, 66.5, 65.2, 63.8, 59.0, 51.4, 20.8, 19.5, 0.3. IR (film): 3029, 2858, 2172, 1495, 1453, 1363, 1248, 1205, 1097, 1071, 1027, 908, 839, 731, 695, 645 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{46}NO_3Si$: 604.324147; found: 604.324106.
(1*R*)-1-*C*-[1-(3-Hydroxypropyl)triazol-4-ylmethyl]-2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-L-arabinitol [(1*R*)-10a]: amber oil; $[\alpha]_D^{20}$ −4.24° ($CHCl_3$, *c* = 1.1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.15–7.35 (m, 21 H), 6.83 (s, 1 H), 4.55 (d, *J* = 12.2 Hz, 1 H), 4.46 (d, *J* = 12.3 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.38 (d, *J* = 12.0 Hz, 1 H), 4.30 (dt, *J* = 6.7, 2.2 Hz, 2 H), 4.25 (d, *J* = 12.1 Hz, 1 H), 4.21 (d, *J* = 11.9 Hz, 1 H), 4.01 (d, *J* = 12.0 Hz, 1 H), 3.93 (br s, 1 H), 3.71–3.78 (m, 2 H), 3.52 (t, *J* = 5.8 Hz, 2 H), 3.43 (dt, *J* = 9.2, 4.5 Hz, 1 H), 3.35 (dd, *J* = 12.0, 8.0 Hz, 1 H), 3.03–3.17 (m, 3 H), 2.92 (dd, *J* = 14.4, 4.4 Hz, 1 H), 1.97 (p, *J* = 6.5 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$/TMS): δ = 145.7, 139.4, 138.7, 138.5, 138.3, 127.7–129.4, 122.1, 82.4, 82.1, 73.0, 71.4, 70.8, 71.9, 69.1, 66.6, 59.0, 58.8, 46.7, 32.6, 25.1. IR (neat): 3342, 2919, 2861, 1453, 1097, 1068 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{45}N_4O_4$: 633.343529; found: 633.343532.
(1*R*)-1-*C*-[1-(3-Hydroxypropyl)triazol-4-ylmethyl]-1,4-dideoxy-1,4-imino-L-arabinitol [(1*R*)-11a]: yellow oil; $[\alpha]_D^{20}$ −4.24° ($CHCl_3$, *c* = 1.1). ^{1}H NMR (400 MHz, CD_3OD/TMS): δ = 7.79 (s, 1 H), 4.47 (t, *J* = 7.0 Hz, 2 H), 3.86 (dd, *J* = 3.7, 1.6 Hz, 1 H), 3.78 (dd, *J* = 4.0, 1.6 Hz, 1 H), 3.68 (dd, *J* = 10.8, 4.4 Hz, 1 H), 3.65 (dd, *J* = 11.2, 4.8 Hz, 1 H), 3.57 (t, *J* = 6.4 Hz, 2 H), 3.44 (dt, *J* = 7.3, 4.0 Hz, 1 H), 3.02 (dd, *J* = 14.7, 7.1 Hz, 1 H), 2.96 (br q, *J* = 4.8 Hz, 1 H), 2.88 (dd, *J* = 14.6, 7.5 Hz, 1 H), 2.09 (p, *J* = 6.5 Hz, 2 H). ^{13}C NMR (101 MHz, CD_3OD/TMS): δ = 146.6, 124.2, 81.2, 79.1, 68.4, 63.5, 62.5, 59.3, 48.2, 34.0, 26.1. IR (neat): 3265, 2922, 1652, 1557, 1429, 1216, 1060 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}N_4O_4$: 273.155732; found: 273.155429.