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Stereoselective synthesis of 1,1′-linked α-L-lyxopyranosyl β-D-glucopyranoside, the proposed biosynthetic precursor of the FG ring system of avilamycins

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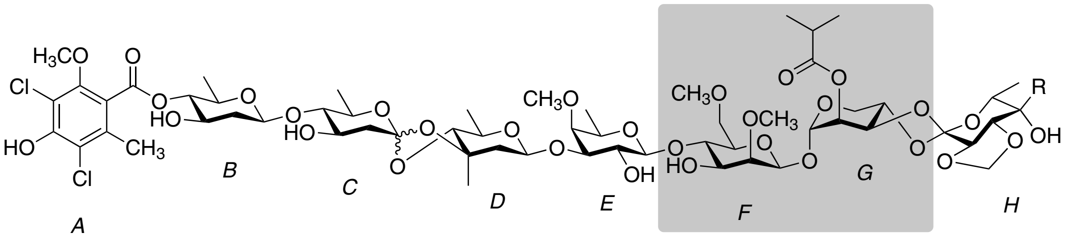
Abstract—The non-reducing disaccharide β-D-Glc*p*-(1↔1)-α-L-Lyx*p* **1** had been proposed to be an early intermediate during the biosynthesis of avilamycin A [Boll, R.; Hofmann, C.; Heitmann, B.; Hauser, G.; Glaser, S.; Koslowski, T.; Friedrich, T.; Bechthold, A. *J. Biol. Chem.* **2006**, *281*, 14756–14763]. This work describes a comparison of two strategies for the synthesis of **1** and its 2-amino-2-deoxy analog with either the glucose or the lyxose moiety acting as the glycosyl donor. The best results in terms of stereoselectivity and yield were obtained with 2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl trichloroacetimidate **13**. Reaction of **13** with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose gave the disaccharide as mixture of 1β,1′α and 1β,1′β isomers in a ratio of 10:1 and a yield of 50%. Reaction of **13** and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranose yielded the desired 1β,1′α disaccharide as a single isomer in 72% yield. Interestingly, the formation of α-glucosides was not observed in any case, regardless of the use of glucose as glycosyl donor or acceptor.

Keywords: Avilamycin A; Glycosylation; Lyxose; Non-reducing disaccharides; Trichloroacetimidates

1. Introduction

The avilamycins are oligosaccharide antibiotics isolated from *Streptomyces viridochromogenes* Tü57. Along with everninomycins, curamycins, and flambamycins, they belong to the orthosomycin group of antibiotics.[1] Avilamycin A, the main compound produced by *S. viridochromogenes* Tü57, was shown to be active against many Gram-positive bacteria, including emerging problem organisms such as vancomycin-resistant enterococci, methicillin-resistant staphylococci, and penicillin-resistant pneumococci.[2] Avilamycin inhibits protein biosynthesis by binding to the 50S ribosomal subunit of bacterial ribosomes.[3–5] Everninomicin (Ziracin), which is structurally very similar to avilamycin, was under investigation for approval by Schering-Plough. Due to



avilamycin A: R = C(O)CH$_3$
avilamycin C: R = CH(OH)CH$_3$

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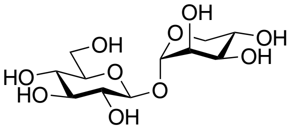
side effects and its poor water solubility, further development was stopped in 2000.[2] Thus, the development of novel strategies for the synthesis of new orthosomycin-type antibiotics with improved properties is of great interest.

Recent research carried out by Bechthold and coworkers led to the conclusion that the non-reducing disaccharide **1** composed of β-D-glucopyranose and α-L-lyxose is an early intermediate during the biosynthesis of avilamycin.[6] At a late stage in the biosynthesis and after having been methylated and acylated at several hydroxy groups, AviX12, a radical AdoMet enzyme, seems to be implicated in epimerizing this disaccharide subunit to its final configuration β-D-Man*p*-(1↔1)-α-L-Lyx*p* (marked in gray in the avilamycin structure), thereby converting avilamycin to its bioactive conformation. It has been shown that inactivation of the gene *aviE2* of *S. viridochromogenes* results in the breakdown of the avilamycin biosynthesis.[7] aviE2 is a decarboxylase that catalyzes the formation of UDP-L-lyxose, which is a biosynthetic step prior to the formation of **1**. Thus, it can be hypothesized that feeding experiments with **1** will lead to resumption of the avilamycin biosynthesis of this mutant. Feeding of analogs of **1** potentially leads to the formation of avilamycin derivatives with improved properties such as higher water solubility. In this report, we describe the stereoselective synthesis of **1** as well as the deoxy-amino analog **2** (Chart 1).

Non-reducing disaccharides are known in nature, with sucrose (β-D-Fru*f*-(2↔1)-α-D-Glc*p*) and trehalose (α-D-Glc*p*-(1↔1)-α-D-Glc*p*) being prominent examples. In contrast to conventional glycoside syntheses, the stereoselective synthesis of non-reducing disaccharides demands for control of stereochemistry at two anomeric centers.[8–21] Accordingly, many syntheses of non-reducing disaccharides lead to mixtures of stereoisomers. In addition, yields in the formation of 1-1′-linked disaccharides significantly exceed 50% only in rare cases. A few examples of their stereoselective synthesis have been reported, including the formation of β-mannoside-containing 1,1′-disaccharides[22] by use of cyclic tin acetals,[23,24] α,α-trehalose[25] by use of intramolecular aglycon delivery[26] and the preparation of sucrose.[27,28] Cook et al. reported the stereoselective synthesis of β,β-trehalose by using the trichloroacetimidate method.[13]



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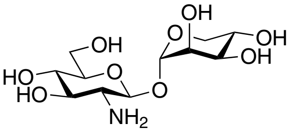
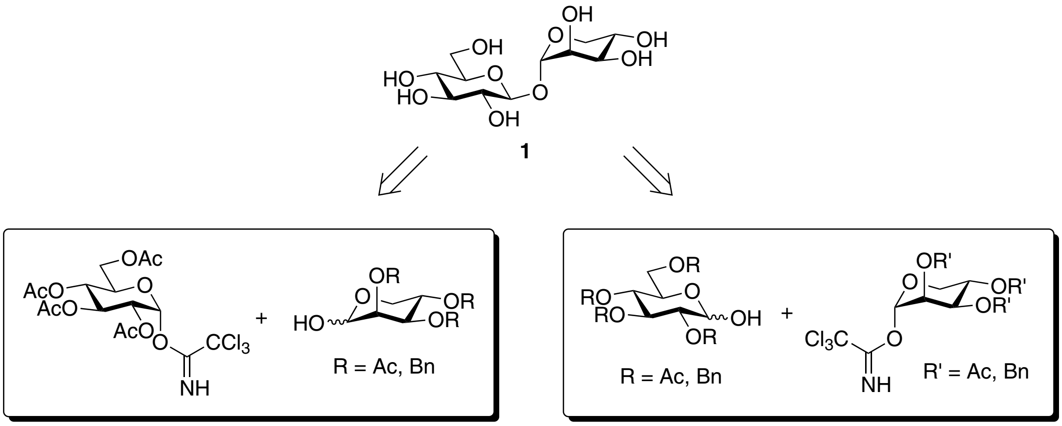


2

Chart 1.

2. Results and discussion

For the synthesis of **1**, we compared two strategies with either the glucose or the lyxose moiety acting as the glycosyl donor (Scheme 1). Because both β-glucopyranosides and α-lyxopyranosides have a 1,2-trans configuration, they should be readily accessible by use of protecting groups with neighboring group participation such as acetyl and benzoyl groups.[29–31] α-Lyxopyranosides were also expected to be preferentially obtained from benzyl protected donors due to the anomeric effect and the steric influence of the protected hydroxy group at the 2-position as is well known for α-mannopyranosides.[32,33] The selectivity at the anomeric center of the glycosyl acceptor was more difficult to predict. From anomeric O-alkylation reactions with gluco- and galactopyranoses under alkaline conditions it is known that an equatorial anomeric OH group often reacts faster and, therefore, β-glucosides may be selectively obtained under kinetic control (kinetic anomeric effect).[30,34,35] However, the base used for anomeric alkoxide formation, chelation control, solvent, and reaction temperature also play a role in determining anomeric stereoselectivity. Anomeric O-alkylation reactions of



Scheme 1. Retrosynthetic strategies investigated for the synthesis of 1,1′-disaccharide **1**.

lyxose have not yet been reported and were not clearly predictable. TMSOTf-catalyzed glycosylation of 2,3,4,6-tetra-*O*-benzyl-D-mannose with a mannosyl trichloroacetimidate, however, predominantly led to an α-glycoside.[22]

L- and D-Lyxose are both commercially available. However, because L-lyxose is significantly more expensive, initial experiments were carried out with the D-isomer. Although it was not expected that the stereoselectivities for the formation of the diastereomeric disaccharides β-D-Glc*p*-(1↔1)-α-L-Lyx*p* and β-D-Glc*p*-(1↔1)-α-D-Lyx*p* are the same due to the possible occurrence of matched/mismatched pairs,[36] at least some valuable lessons were expected to be learned from these experiments.

2.1. Preparation of glycosyl donors and acceptors

Glucose derivatives **3**,[37] **4**,[38] **5**,[39] **6**, and **7**[38] and D-lyxose derivatives **8**[40,41] and **9**[42,43] were obtained according to published procedures or were commercially available (**6**, Chart 2). The synthesis of the required L-lyxose derivatives is shown in Scheme 2. Peracetylated L-lyxopyranose **11**[44] obtained from L-lyxose **10** by treatment with acetic anhydride and pyridine was selectively deprotected at the anomeric center using the method of Zhang and Kováč[39] to give **12**. Reaction with trichloroacetonitrile and potassium carbonate[45] gave α-trichloroacetimidate **13** in a yield of 83%. Methyl glycoside **14**,[46,47] obtained by Fischer glycosylation[42] of L-lyxose **10**, was further processed similar to a procedure reported for the preparation of the D-*lyxo* isomer of **16**.[43] Thus, **14** was benzylated with benzyl bromide and KOH followed by cleavage of the crude methyl glycoside **15** under acidic conditions to give **16** in a yield of 82%. Compound **16** was converted to trichloroacetimidate **17**, which turned out to be too reactive to be either purified by column chromatography or stored for a prolonged time. Thus, it was freshly prepared before each experiment and immediately used without further purification.

2.2. Glycosylations with glucosyl donors

To explore suitable reaction conditions for the formation of 1,1′-disaccharides, glucosyl trichloroacetimidate **3** was reacted with acetylated D-lyxose acceptor **8** in dichloromethane under varying reaction conditions (Scheme 3). As expected, the formation of α-glucosides was not observed in any case. The glycosidic linkage at the D-lyxose was formed as a mixture of α- and β-anomers. Table 1 gives an overview of the ratio of products **18** (1β,1′α-configuration) and **19** (1β,1′β-configuration). The use of TMSOTf gave low yields and low stereoselectivities regardless of the amount of Lewis acid added (entries 1–3). Switching to tin tetrachloride slightly improved yield and stereoselectivity (entries 4–6). Best results were obtained with $BF_3 \cdot OEt_2$ (entries 7–11) with yields up to 45% and an **18**/**19** ratio of 4:1. Ratios of products **18**/**19** were determined from ^1H NMR spectra of the isolated product mixtures.

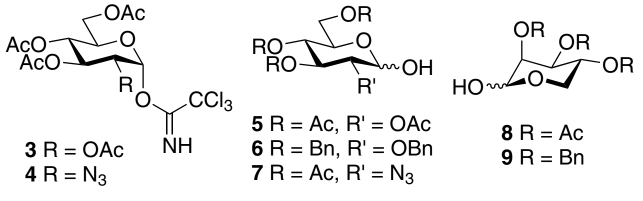
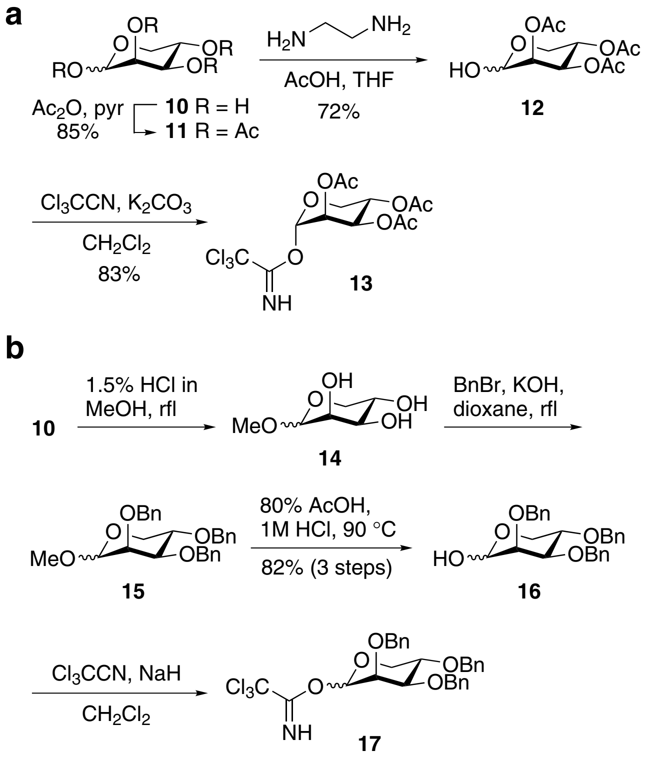
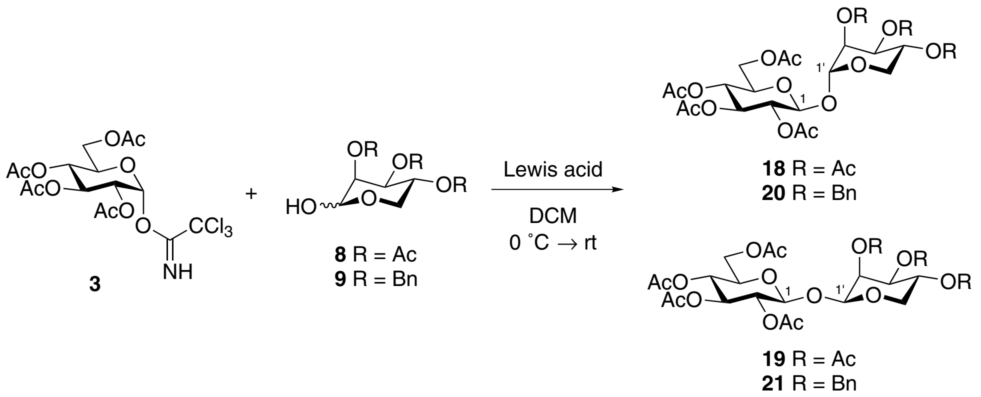


Chart 2.



Scheme 2. Synthesis of L-lyxose derivatives **13** (a) and **17** (b).

The anomeric configurations of the products **18** and **19** were determined by NMR spectroscopy. Whereas the β-configuration of the glucose residues could be readily deduced from $^3J_{\text{H-1,H-2}}$ coupling constants (**18**: 8.4 Hz, **19**: 8.0 Hz), $^1J_{\text{C-1}',\text{H-1}'}$ coupling constants obtained from non-decoupled heteronuclear single quantum coherence (HSQC) NMR spectra were used for determination of the lyxose configuration. It is well established that α-mannosides and α-rhamnosides have higher $^1J_{\text{C-1,H-1}}$ values (usually higher than 170 Hz) than the corresponding β-glycosides (usually lower than 170 Hz),[48–50] and it can be assumed that this trend is also applicable to lyxose. Thus, we assigned the product with the $^1J_{\text{C-1}',\text{H-1}'}$ value of 174.1 Hz to be α-lyxoside **18** and that with the value of 170.2 Hz to be the β-lyxoside **19**.



Scheme 3. Synthesis of D-lyxopyranosyl β-D-glucopyranosides **18**–**21**.

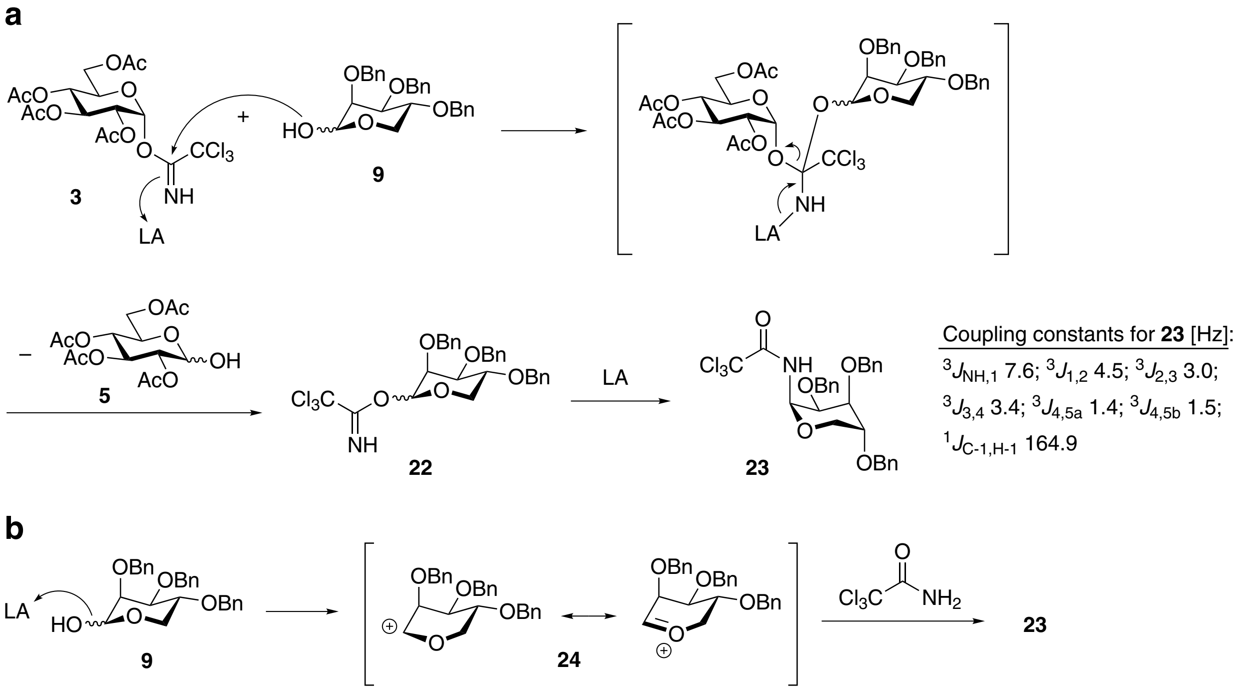
Table 1. Results of glycosylation reactions of **3** and **8** according to Scheme 3

Entry	**3** (equiv)	**8** (equiv)	Lewis acid	Lewis acid (equiv)	Yield (%)	**18/19**
1	1	1.05	TMSOTf	0.1	19	2:1
2	1	1.05	TMSOTf	0.5	17	2:1
3	1	1.05	TMSOTf	1	24	2:1
4	1.1	1	$SnCl_4$	0.1	31	3.5:1
5	1.1	1	$SnCl_4$	0.5	31	3.5:1
6	1.1	1	$SnCl_4$	1	31	3.5:1
7	1	1.05	$BF_3{\cdot}OEt_2$	0.1	39	4:1
8	1	1.05	$BF_3{\cdot}OEt_2$	0.25	31	4:1
9	1	1.05	$BF_3{\cdot}OEt_2$	0.5	45	4:1
10	1	1.05	$BF_3{\cdot}OEt_2$	1	40	4:1
11	1	1.05	$BF_3{\cdot}OEt_2$	2	36	4:1

To study the influence of the protecting groups of the glycosyl acceptor, trichloroacetimidate **3** was also reacted with benzylated lyxose acceptor **9** (Scheme 3). As can be seen from the results in Table 2, only the use of tin tetrachloride as Lewis acid resulted in product formation, this time, however, with an increased

Table 2. Results of glycosylation reactions of **3** and **9** according to Scheme 3

Entry	**3** (equiv)	**9** (equiv)	Lewis acid	Lewis acid (equiv)	Yield (%)	**20/21**
1	1.4	1	TMSOTf	0.1	—	—
2	1.4	1	$BF_3{\cdot}OEt_2$	0.1	—	—
3	1.4	1	$SnCl_4$	0.1	45	10:1



Scheme 4. Possible mechanisms for the formation of **23**. LA = Lewis acid.

stereoselectivity of **20**/**21** = 10:1. Using the stronger Lewis acids TMSOTf and $BF_3{\cdot}OEt_2$, respectively, no disaccharide formation was observed. Instead, 2,3,4-tri-*O*-benzyl-β-D-lyxopyranosyl trichloroacetamide **23**, which according to NMR analysis exists in a $^1C_4$ conformation, was isolated in a yield of 70%. The formation of **23** may be rationalized by nucleophilic attack of tri-*O*-benzyl-lyxose **9** to trichloroacetimidate **3** in a Lewis acid-catalyzed process outlined in Scheme 4a followed by release of tetra-*O*-acetyl-glucose **5** and rearrangement of trichloroacetimidate **22**. Such rearrangements of trichloroacetimidates to trichloroacetamides are well known in carbohydrate chemistry and recently have been applied in the preparation of glycosyl amines.[51] More likely, however, is the Lewis acid-promoted formation of lyxosyl cation **24** from either reactive **9** or by cleavage of intermediately formed disaccharide **20** (or **21**) and subsequent reaction with trichloroacetamide to yield **23** (Scheme 4b). Trichloroacetamide is produced during the glycosylation reaction or hydrolysis of **3** with the water stemming from activation of **9**. To examine the mechanism depicted in Scheme 4b, tribenzyl lyxose **9** was reacted with trichloroacetamide and $BF_3{\cdot}OEt_2$ (0.1 equiv) under the same reaction conditions employed above. After 12 h, lyxopyranosyl trichloroacetamide **23** was obtained in 60% yield, supporting the postulated mechanism.

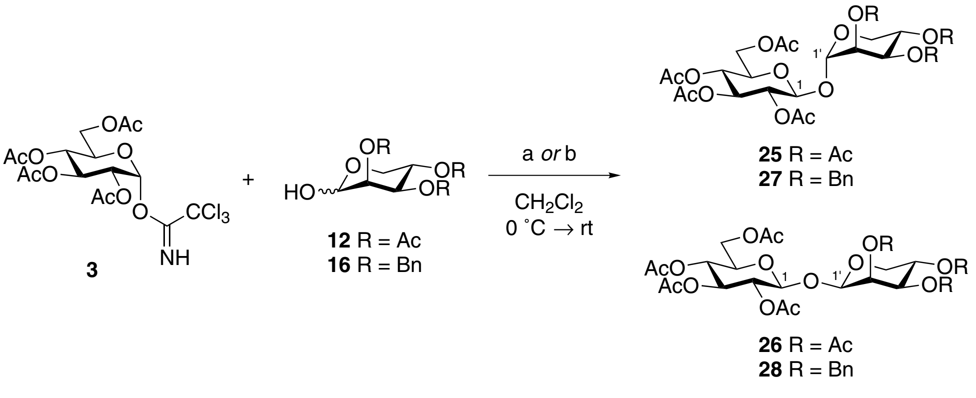
We next turned our attention to glycosylation reactions with lyxose acceptors having the desired L-configuration (Scheme 5). Thus, glucosyl trichloroacetimidate **3** was treated with **12** and **16**, respectively, and the Lewis acid that turned out to be best for reactions with the corresponding D-isomers. Reaction of **3** and acetylated acceptor **12** with $BF_3{\cdot}OEt_2$ (0.1 equiv) gave the disaccharides **25** and **26** in an improved yield of 52%, however, with a reduced stereoselectivity of **25**/**26** = 1.5:1. Glycosylation of benzylated acceptor **16** with trichloroacetimidate **3** and $SnCl_4$ (0.03 equiv) resulted in disaccharides **27** and **28** in a yield of 48% and a 1β,1′α/1β,1′β ratio of 7:1.

2.3. Glycosylations with lyxosyl donors

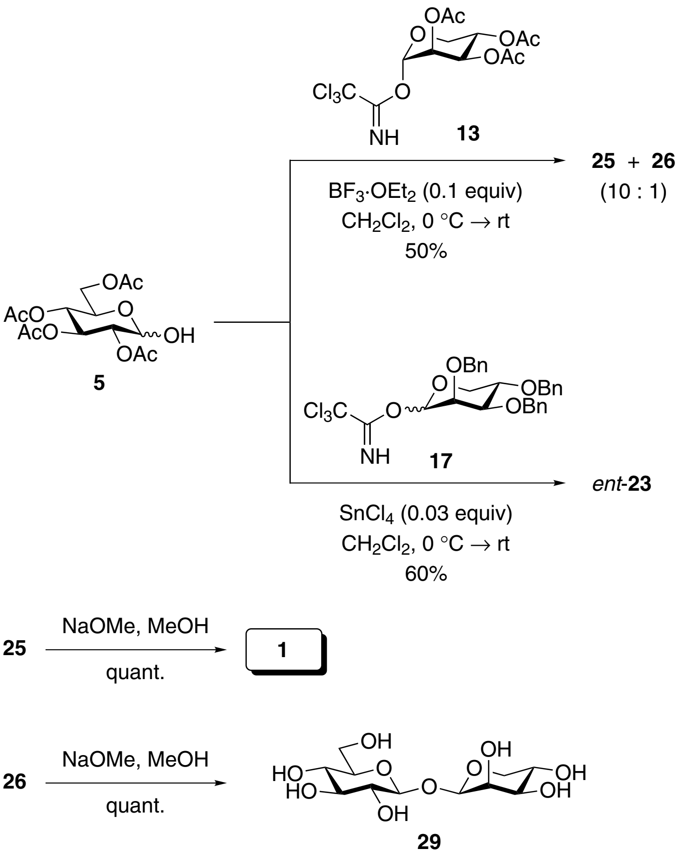
Scheme 6 shows the results obtained with L-lyxosyl trichloroacetimidates **13** and **17**, and tetra-*O*-acetyl-glucose **5**. Reaction of acetylated L-lyxosyl donor **13** gave two isomeric disaccharides in a ratio of 10:1, and a combined yield of 50%. As expected, the major isomer was 1β,1′α compound **25**. To our surprise, however, the minor isomer turned out to be 1β,1′β compound **26**. Isomers with an α-glucose configuration could not be observed. This indicates on one hand that the kinetic anomeric effect, that is, the higher reactivity of the β-anomer of **5** compared to the α-anomer, is very effective for this pair of glycosyl donor and acceptor. On the other hand, it becomes obvious that the stereochemistry at the lyxose moiety is not fully controlled either by the neighboring group effect of the 2-*O*-acetyl group or by the anomeric effect both of which would favor α-lyxose configuration. In this respect, it is worth mentioning that reaction of **13** with the more nucleophilic glycosyl acceptor tetra-*O*-benzyl-glucose **6** leads to a ratio of the 1β,1′α and 1β,1′β isomers of only 3:1 (data not shown), which can be explained by an increased S_N2 character of the reaction. Attempts to react glucose acceptor **5** with the reactive benzylated L-lyxosyl donor **17** were unsuccessful, even with the mild Lewis acid tin tetrachloride. In this case, the trichloroacetimidate-to-trichloroacetamide rearrangement was too fast leading to formation of the enantiomer of **23** in approximately 60% yield (Scheme 6). The mixture of **25** and **26** was separated by HPLC and the pure isomers were deacetylated under Zemplén conditions to give α-L-lyxopyranosyl β-D-glucopyranoside **1** and its 1β,1′β isomer **29** in quantitative yields.

2.4. Preparation of amino-substituted disaccharide 2

The preparation of amino-deoxy disaccharide **2** is shown in Scheme 7. When 2-azido-glucopyranosyl trichloroacetimidate **4** was reacted with lyxose acceptor **12**, the desired 1β,1′α isomer **30** was formed in 41% yield

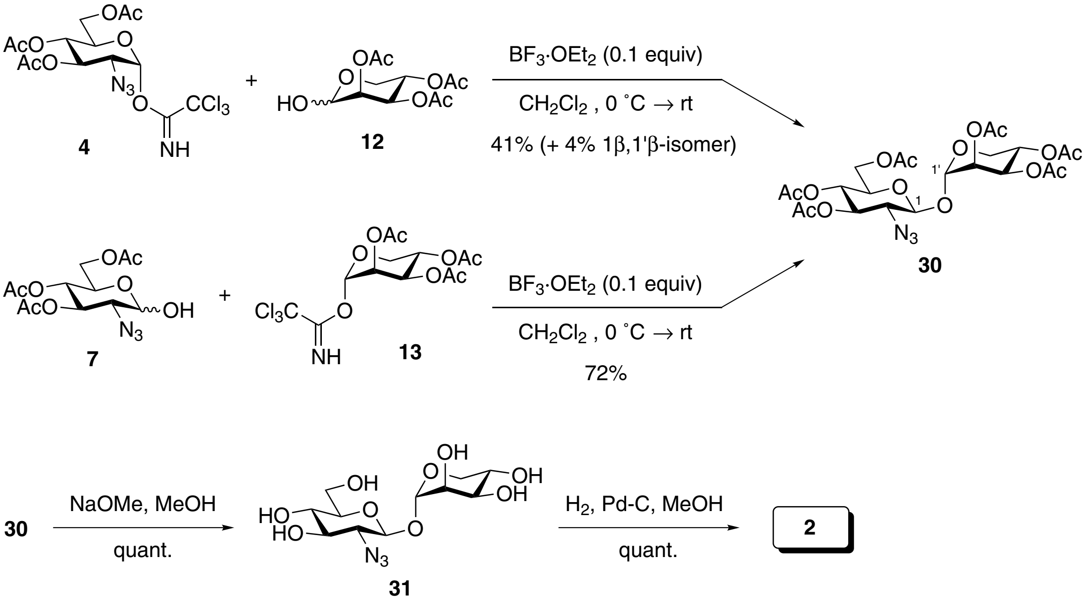


Scheme 5. Synthesis of L-lyxopyranosyl β-D-glucopyranosides **25**–**28**. Reagents: (a) **3**, **12** (1.1 equiv), $BF_3{\cdot}OEt_2$ (0.1 equiv) (52%, **25**/**26** = 1.5:1); (b) **3** (1.4 equiv), **16**, $SnCl_4$ (0.03 equiv) (48%, **27**/**28** = 7:1).



Scheme 6. Glycosylations with L-lyxosyl donors **13** and **17**.

in addition to small amounts of the 1β,1′β isomer (1β,1′α/1β,1′β = 10:1). Using 2-azido-2-deoxy-glucose **7** and L-lyxosyl trichloroacetimidate **13**, disaccharide **30** was obtained as single isomer in a yield of 72%. In both cases, the formation of an α-glucosidic linkage was not observed. Finally, **30** was deacetylated followed by reduction of the azide group by catalytic hydrogenation to give disaccharide **2** in quantitative yields.



Scheme 7. Synthesis of α-L-lyxopyranosyl 2-amino-2-deoxy-β-D-glucopyranoside **2**.

3. Conclusions

In summary, two strategies for the synthesis of non-reducing disaccharides **1** and **2** were compared with either the glucose or the lyxose moiety acting as the glycosyl donor. For both **1** and **2** the application of lyxosyl trichloroacetimidate **13** turned out to be superior over the use of a glucosyl donor in terms of stereoselectivity and yield. Using $BF_3{\cdot}OEt_2$ as the Lewis acid, reaction of **13** and tetra-*O*-acetyl-glucopyranose **5** gave protected disaccharides **25** and **26** in a ratio of 10:1 and a yield of 50%. Reaction of **13** with 2-azido-2-deoxy-glucopyranose **7** resulted in the formation of disaccharide **30** as a single stereoisomer in a yield of 72%. Interestingly, the formation of α-glucosides was not observed in any case, regardless of the use of glucose as glycosyl donor or acceptor whereas reaction of neighboring-group active lyxosyl donor **13** only in one case led to exclusive formation of a 1,2-*trans*-glycoside (**30**). Both disaccharides β-D-Glc*p*-(1↔1)-α-L-Lyx*p* and its 2-azido-2-deoxy analog were deprotected in quantitative yields. Currently, **1** and **2** are being subjected to feeding experiments with a *S. viridochromogenes* strain with inactivated *aviE*2 gene and results will be reported in due course.

4. Experimental

4.1. General methods

TLC was carried out on Silica Gel 60 F_{254} (Merck, layer thickness 0.2 mm) with detection by UV light ($\lambda = 254$ nm) and/or by charring with 15% sulfuric acid in ethanol. Flash column chromatography (FC) was performed on Merck Silica Gel 60 (0.040–0.063 mm) with the solvent systems specified. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 250 and Bruker Avance DRX 600 instruments. Chemical shifts are reported in ppm relative to solvent signals: $CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.0$ ppm; DMSO-d_6: $\delta_H = 2.49$ ppm, $\delta_C = 39.7$ ppm; CD_3OD: $\delta_H = 4.78$ ppm, $\delta_C = 49.3$ ppm. Signals were assigned by first-order analysis and, when feasible, assignments were supported by two-dimensional ^{1}H, ^{1}H and ^{1}H, ^{13}C correlation spectroscopy. $^1J_{H-C}$ coupling constants were obtained from non-decoupled heteronuclear single quantum coherence (HSQC) NMR spectra. $^3J_{H-H}$ and $^1J_{H-C}$ coupling constants are reported in Hz. Within disaccharides, signals of lyxose residues are labeled with primed numbers. MALDI-TOF mass spectra were recorded on a Bruker Biflex III spectrometer with α-cyano-4-hydroxy-cinnamic acid (CHCA) as the matrix. ESI-IT mass spectra were recorded on a Bruker Esquire 3000 spectrometer. Elemental analysis was performed on an elementar CHNS vario EL instrument. RP-HPLC was performed on a LC-20A prominence system from Shimadzu. Used columns: Nucleosil 100-5 C-18 (analytical: 4 × 250 mm, flow 0.9 mL min^{-1}, semi-preparative 8 × 250 mm, flow 3 mL min^{-1}) from Knauer. Eluent: gradient of water with 0.1% TFA (eluent A) in acetonitrile with 0.1% TFA (eluent B).

4.2. 2,3,4-Tri-*O*-acetyl-α/β-L-lyxopyranose (12)

To a solution of ethylenediamine (0.5 mL, 8.8 mmol) in tetrahydrofuran (50 mL), acetic acid (0.5 mL, 7.5 mmol) was added slowly upon which a white precipitate occurred. Then 1,2,3,4-tetra-*O*-acetyl-α/β-L-lyxopyranose **11**[44] (3.5 g, 11 mmol), which had been prepared from L-lyxose **10** by treatment with Ac_2O and pyridine according to a published procedure,[52] was added and the mixture was stirred for 16 h at room temperature. After addition of water (50 mL) the precipitate dissolved completely. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with 1 N HCl (50 mL), satd aq $NaHCO_3$ (50 mL), and water (50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 3:2) yielded **12** (2.2 g, 72%) as a colorless oil. Preparation of the D-*lyxo* isomer of **12** had been reported earlier.[40,41]

$R_f = 0.28$ (petroleum ether–EtOAc 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.40 (dd, $J = 8.3$, 3.6, 1H, H-3), 5.20 (‘t’, $J = 3.6$, 1H, H-2), 5.13–5.06 (m, 2H, H-1 and H-4), 3.91–3.86 (m, 2H, H-5a, H-5b), 2.12 (s, 3H, $C(O)CH_3$), 2.08 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$); (MALDI-TOF-MS): *m*/*z* 299.2 $[M+Na]^+$, 315.2 $[M+K]^+$; Anal. Calcd for $C_{11}H_{16}O_8$: C, 47.83; H, 5.84. Found: C, 48.17; H, 5.79.

4.3. 2,3,4-Tri-*O*-acetyl-α-L-lyxopyranosyl trichloroacetimidate (13)

To a solution of **12** (0.5 g, 1.8 mmol) and trichloroacetonitrile (0.63 mL, 6 mmol) in dry CH_2Cl_2 (10 mL) K_2CO_3 (0.63 g, 4.6 mmol) was added and the mixture was stirred for 1.5 h. The reaction mixture was filtered, concentrated, and the residue was purified by FC (petroleum ether–EtOAc 2:1) to give **13** as colorless oil (0.63 g, 83%). The preparation of the D-*lyxo* isomer of **13** with trichloroacetonitrile–DBU in a yield of 68% had been reported earlier.[41] $R_f = 0.33$ (petroleum ether–EtOAc 2:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 8.75 (br s, 1H, NH), 6.18 (d, $J = 2.5$, 1H, H-1), 5.46–5.37 (m, 2H, H-2, H-3), 5.32–5.28 (m, 1H, H-4), 4.06 (dd, $J = 11.3$, 5.2, 1H, H-5a), 3.82 (dd, $J = 11.3$, 9.6, 1H, H-5b), 2.16 (s, 3H, $C(O)CH_3$), 2.07 (s, 3H, $C(O)CH_3$), 2.04 (s, 3H, $C(O)CH_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 169.7 ($C(O)CH_3$), 169.6 ($C(O)CH_3$), 160.2 ($C(O)CH_3$), 94.6 (C-1), 67.8 (C-2), 68.2 (C-3), 66.0 (C-4), 62.0 (C-5), 21.0 ($C(O)CH_3$), 20.8 ($C(O)CH_3$), 20.7 ($C(O)CH_3$);

$^1J_{\text{H-1,C-1}} = 179.9$; (MALDI-TOF-MS): *m*/*z* 443.3 [*M*+Na]$^+$, 459.2 [*M*+K]$^+$; Anal. Calcd for $C_{13}H_{16}Cl_3NO_8$: C, 37.12; H, 3.83; N, 3.33. Found: C, 37.59; H, 4.28; N, 3.22.

4.4. 2,3,4-Tri-*O*-benzyl-α/β-L-lyxopyranose (16)

Under a N_2 atmosphere, acetyl chloride (0.7 mL, 9.8 mmol) was dissolved in MeOH (30 mL). L-Lyxose **10** (2 g, 13.3 mmol) was added and the reaction mixture was stirred under reflux for 2 h. After neutralization with 0.5 M sodium methylate solution in MeOH the reaction mixture was concentrated. The residue was dissolved in dioxane (15 mL) and suspended with KOH (9 g, 0.16 mol) under reflux. Benzyl bromide (16 mL, 0.13 mol) was added dropwise and after 4 h under reflux the reaction mixture was concentrated. After addition of water (50 mL) the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was added to 80% aq AcOH (90 mL). After addition of 1 N HCl (35 mL), the mixture was heated for 10 h at 90 °C. Then the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 3:1) yielded **16** (4.6 g, 82%) as a colorless oil. Preparation of the D-*lyxo* isomer of **16** by similar procedures had been reported earlier.[42,43] $R_f = 0.25$ (petroleum ether–EtOAc 2:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): α-anomer: δ 7.39–6.26 (m, 15H, Ph), 5.18 (dd, *J* = 10.1, 2.1, 1H, H-1), 5.01 (br d, *J* = 10.1, 1H, OH), 4.77–4.48 (m, 6H, CH_2), 4.08 (dd, *J* = 12.6, 1.2, 1H, H-5a), 3.92–3.90 (m, 1H, H-3), 3.88 (‘t’, *J* = 3, 1H, H-2), 3.63–3.61 (m, 1H, H-5b); β-anomer: δ 7.39–6.26 (m, 15H, Ph), 5.12 (d, *J* = 2.1, 1H, H-1), 4.77–4.48 (m, 6H, CH_2), 3.91 (m, 1H, H-3), 3.85 (m, 1H, H-4), 3.81 (m, 2H, H-5a, H-5b), 3.73 (‘t’, *J* = 3.6, H-2); ^{13}C NMR (150.9 MHz, $CDCl_3$): α-anomer: δ 138.6 (quaternary C), 138.5 (quaternary C), 138.3 (quaternary C), 128.5–127.4 (aromatic C), 93.0 (C-1), 76.6 (C-3), 74.4 (C-4), 72.9 (C-2), 74.5 (*C*H$_2$Ph), 74.2 (*C*H$_2$Ph), 74.2 (*C*H$_2$Ph), 56.6 (C-5); $^1J_{\text{H-1,C-1}} = 170.0$; β-anomer: δ 93.9 (C-1); $^1J_{\text{H-1,C-1}} = 165.9$; (MALDI-TOF-MS): *m*/*z* 443.3 [*M*+Na]$^+$, 459.2 [*M*+K]$^+$; Anal. Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 73.87; H, 6.89.

4.5. 2,3,4-Tri-*O*-acetyl-α-D-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (18) and 2,3,4-tri-*O*-acetyl-β-D-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (19)

Compounds **3**[37] (100 mg, 0.2 mmol) and **8**[40,41] (60 mg, 0.21 mmol) were dissolved at 0 °C in dry CH_2Cl_2 (2 mL). A solution of $BF_3{\cdot}OEt_2$ (11 μL, 0.1 mmol) in dry CH_2Cl_2 (0.25 mL) was added and the mixture was stirred for 14 h at rt. The mixture was diluted with CH_2Cl_2 (20 mL), washed with satd aq $NaHCO_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried ($MgSO_4$), and concentrated. Purification by FC (petroleum ether–EtOAc 2:1) yielded a 4:1 mixture of **18** and **19** (49 mg, 45%) as a colorless oil. $R_f = 0.19$ (petroleum ether–EtOAc 1:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): **18**: δ 5.27 (dd, *J* = 9.6, 3.6, 1H, H-3′), 5.20–5.16 (m, 2H, H-3, H-4′), 5.10–5.05 (m, 2H, H-4, H-2′), 5.01 (dd, *J* = 9.6, 8.4, 1H, H-2), 4.93 (d, *J* = 2.4, 1H, H-1′), 4.66 (d, *J* = 8.4, 1H, H-1), 4.23 (dd, *J* = 12.6, 4.8, 1H, H-6a), 4.08 (dd, *J* = 12.6, 2.4, 1H, H-6b), 3.84–3.80 (m, 2H, H-5a′, H-5b′), 3.70 (m, 1H, H-5), 2.12 (s, 3H, C(O)CH_3), 2.08 (s, 6H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 2.02 (s, 3H, C(O)CH_3), 2.01 (s, 3H, C(O)CH_3), 2.00 (s, 3H, C(O)CH_3); **19**: δ 5.42 (‘t’, *J* = 9.8, 1H, H-3), 5.32 (dd, *J* = 9.5, 3.5, 1H, H-3′), 4.76 (d, *J* = 8.0, 1H, H-1), 3.68 (ddd, *J* = 10.2, 5.2, 2.4, 1H, H-5), 3.53 (dd, *J* = 12.6, 3.3, 1H, H-5a′), 2.09 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 2.00 (s, 3H, C(O)CH_3); ^{13}C NMR (150.9 MHz, $CDCl_3$): **18**: δ 170.7–169.6 (7 × s, *C*(O)CH_3), 99.9 (C-1), 98.4 (C-1′), 72.5 (C-3), 72.3 (C-5), 71.1 (C-2), 69.1 (C-2′), 68.0 (C-4), 67.9 (C-3′), 66.5 (C-4′), 61.7 (C-6), 60.6 (C-5′), 20.9–20.7 (s, 7 × C(O)*C*H$_3$); $^1J_{\text{H-1}',\text{C-1}'} = 174.1$; $^1J_{\text{H-1,C-1}} = 166.3$; **19**: δ 96.0 (C1), 92.9 (C1′); $^1J_{\text{H-1}',\text{C-1}'} = 170.2$; $^1J_{\text{H-1,C-1}} = 166.3$; (MALDI-TOF-MS): *m*/*z* 629.2 [*M*+Na]$^+$, 645.2 [*M*+K]$^+$; Anal. Calcd for $C_{25}H_{34}O_{17}$: C, 49.51; H, 5.65. Found: C, 49.12; H, 6.04.

4.6. 2,3,4-Tri-*O*-benzyl-α-D-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (20) and 2,3,4-tri-*O*-benzyl-β-D-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (21)

Compounds **3**[37] (246 mg, 0.5 mmol) and **9**[42,43] (150 mg, 0.35 mmol) were dissolved at 0 °C in dry CH_2Cl_2 (2 mL). A solution of $SnCl_4$ (1 M in CH_2Cl_2, 35 μL, 0.035 mmol) was added and the mixture was stirred for 20 h at rt. The mixture was diluted with CH_2Cl_2 (20 mL), washed with satd aq $NaHCO_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 2:1) yielded a 10:1 mixture of **20** and **21** (120 mg, 45%) as a colorless oil. $R_f = 0.34$ (petroleum ether–EtOAc 3:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): **20**: δ 7.37–7.27 (m, 15H, Ph), 5.16 (‘t’, 9.6, 1H, H-3), 5.08 (‘t’, *J* = 9.6, 1H, H-4), 4.97 (dd, *J* = 9.6, 8.4, 1H, H-2), 4.86 (d, *J* = 3.6, 1H, H-1′) 4.75–4.77 (m, 6H, CH_2), 4.64–4.61 (m, 1H, H-1), 4.26 (dd, *J* = 12.6, 4.8, 1H, H-6a), 4.09 (dd, *J* = 12.6, 2.4, 1H, H-6b), 3.93 (m, 1H, H-4′), 3.81 (dd, *J* = 8.4, 3.6, 1H, H-3′), 3.76 (m, 2H, H-5a′, H-5b′), 3.63 (‘t’, *J* = 3.6, 1H, H-2′), 3.70 (m, 1H, H-5), 2.06 (s, 3H, C(O)CH_3), 2.02 (s, 3H, C(O)CH$_3$), 2.00 (s, 3H, C(O)CH$_3$), 1.83 (s, 3H, C(O)CH$_3$); ^{13}C NMR (150.9 MHz, CDCl$_3$): **20**: δ 170.3 (*C*(O)CH$_3$), 169.4 (*C*(O)CH$_3$), 169.1 (*C*(O)CH$_3$), 169.0 (*C*(O)CH$_3$), 138.6 (quaternary C), 138.5 (quaternary C), 138.2 (quaternary C), 128.5–127.7 (aromatic C), 100.6 (C-1′), 99.8 (C-1), 78.7 (C-3′), 74.8 (C-2′), 74.7 (C-4′), 72.8 (C-3), 72.1 (C-5), 71.4 (C-2), 68.1 (C-4), 62.3 (C-5′), 61.8 (C-6), 20.8 (s C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 20.5 (C(O)*C*H$_3$); $^1J_{\text{H-1}',\text{C-1}'} = 170.0$; $^1J_{\text{H-1},\text{C-1}} = 160.6$; **21**: δ 99.8 (C-1), 95.5 (C1′); $^1J_{\text{H-1}',\text{C-1}'} = 164.2$; $^1J_{\text{H-1},\text{C-1}} = 160.8$; (MALDI-TOF-MS): *m*/*z* 773.4 [*M*+Na]$^+$, 789.4 [*M*+K]$^+$; Anal. Calcd for $C_{40}H_{46}O_{14}$: C, 63.99; H, 6.18. Found: C, 63.57; H, 6.04.

4.7. *N*-(2,3,4-Tri-*O*-benzyl-β-D-lyxopyranosyl)-trichloroacetamide (23)

To a solution of 2,3,4-tri-*O*-benzyl-D-lyxopyranose **9**[42,43] (200 mg, 0.48 mmol) in dry CH$_2$Cl$_2$ (3 mL) was added BF$_3$·OEt$_2$ (6 μL, 0.048 mmol) and trichloroacetamide (81 mg, 0.5 mmol). The reaction mixture was stirred for 12 h. After neutralization and evaporation, purification by FC (petroleum ether–EtOAc 7:1) yielded **23** as a colorless oil (160 mg, 60%). $R_f = 0.55$ (petroleum ether–EtOAc 2:1); ^{1}H NMR (600.1 MHz, CDCl$_3$): δ 8.79 (d, *J* = 7.6, 1H, NH), 7.38–7.27 (m, 15H, Ph), 5.65 (dd, *J* = 7.6, 4.5, 1H, H-1); 4.67–4.48 (m, 6H, CH$_2$), 4.07 (dd, *J* = 4.5, 3.0, 1H, H-2), 3.96 (‘t’, J = 3.4; 1H, H-3), 3.93 (dd, *J* = 12.9, 1.4, 1H, H-5a), 3,71 (dd, *J* = 13.1, 1.5, 1H, H-5b), 3.66 (ddd, *J* ≈ 3.9, 2.0, 1.9, 1H, H-4); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 162.5 (C=O), 137.6 (quaternary C), 137.5 (quaternary C), 137.0 (quaternary C), 128.5–127.7 (aromatic C), 76.8 (C-1), 76.1 (C-3), 74.0 (C-4), 71.0 (C-2), 74.5 (*C*H$_2$Ph), 74.1 (*C*H$_2$Ph), 74.1 (*C*H$_2$Ph), 58.6 (C-5); $^1J_{\text{H-1},\text{C-1}} = 164.9$; (ESI-IT-MS): *m*/*z* 686.6 [*M*+Na]$^+$, 602.6 [*M*+K]$^+$; Anal. Calcd for $C_{28}H_{28}Cl_3NO_5$: C, 59.53; H, 5.00, N, 2.48. Found: C, 59.13; H, 5.03, N, 2.50.

4.8. 2,3,4-Tri-*O*-acetyl-α-L-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (25) and 2,3,4-tri-*O*-acetyl-β-L-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (26)

4.8.1. Method a. Compounds **3**[37] (764 mg, 1.55 mmol) and **12** (450 mg, 1.61 mmol) were dissolved at 0 °C in dry CH$_2$Cl$_2$ (8 mL). BF$_3$·OEt$_2$ (20 μL, 0.16 mmol) was added and the mixture was stirred for 17 h at rt. The mixture was diluted with CH$_2$Cl$_2$ (20 mL), washed with satd aq NaHCO$_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried (MgSO$_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 2:1) yielded a 1.5:1 mixture of **25** and **26** (490 mg, 52%) as a white solid.

4.8.2. Method b. Compounds **13** (970 mg, 2.31 mmol) and **5**[39] (730 mg, 2.1 mmol) were dissolved at 0 °C in dry CH$_2$Cl$_2$ (10 mL). BF$_3$·OEt$_2$ (29 μL, 0.23 mmol) was added and the mixture was stirred for 18 h at rt. The mixture was diluted with CH$_2$Cl$_2$ (20 mL), washed with satd aq NaHCO$_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried (MgSO$_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 2:1) yielded a 10:1 mixture of **25** and **26** (640 mg, 50%) as a white solid. $R_f = 0.23$ (petroleum ether–EtOAc 3:2); (MALDI-TOF-MS): *m*/*z* 629.3 [*M*+Na]$^+$, 645.3 [*M*+K]$^+$; Anal. Calcd for $C_{25}H_{34}O_{17}$: C, 49.51; H, 5.65. Found: C, 49.80; H, 6.10.

The diastereoisomers **25** and **26** were separated by RP-HPLC (40–90% B over 30 min).

Compound **25**: RP-HPLC (semi-preparative column): $t_R = 7.6$ min; ^{1}H NMR (600.1 MHz, CDCl$_3$): δ 5.32 (dd, 1H, *J* = 3.0, 2.4, H-2′), 5,23 (ddd, *J* = 9.9, 9.8, 5.6, 1H, H-4′), 5.19 (dd, *J* = 9.9, 3.3, 1H, H-3′), 5.22 (‘t’, *J* = 9.4, 1H, H-3) 5.13 (‘t’, *J* = 9.6, 1H, H-4), 5.12 (d, *J* = 2.2, 1H, H-1′), 5.09 (dd, *J* = 9.8, 8.2, 1H, H-2), 4.81 (d, *J* = 7.8, 1H, H-1), 4.26 (dd, *J* = 12.6, 4.8, 1H, H-6a), 4,13 (dd, *J* = 12.6, 2.4, 1H, H-6b), 3.93 (dd, *J* = 10.2, 5.4, 1H, H-5a′), 3.72 (m, 1H, H-5), 3.54 (‘t’, *J* = 10.2, 1H, H-5b′), 2.10 (s, 6H, C(O)CH$_3$), 2.07 (s, 3H, C(O)CH$_3$), 2.03 (s, 3H, C(O)CH$_3$), 2.02 (s, 3H, C(O)CH$_3$), 2.01 (s, 3H, C(O)CH$_3$), 2.00 (s, 3H, C(O)CH$_3$); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 170.8 (*C*(O)CH$_3$), 170.4 (*C*(O)CH$_3$), 170.0 (*C*(O)CH$_3$), 169.6 (*C*(O)CH$_3$), 169.4 (*C*(O)CH$_3$), 169.4 (*C*(O)CH$_3$), 168.8 (*C*(O)CH$_3$), 95.0 (C-1), 94.0 (C-1′), 72.6 (C-3′), 72.1 (C-5), 70.8 (C-2), 68.7 (C-2′), 67.9 (C-3), 67.8 (C-4), 66.4 (C-4′), 61.5 (C-6), 60.0 (C-5′), 20.8 (C(O)*C*H$_3$), 20.8 (C(O)*C*H$_3$), 20.7 (C(O)*C*H$_3$), 20.7 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 20.5 (C(O)*C*H$_3$); $^1J_{\text{H-1}',\text{C-1}'} = 175.5$; $^1J_{\text{H-1},\text{C-1}} = 162.8$.

Compound **26**: RP-HPLC (semi-preparative column): $t_R = 6.6$ min; ^{1}H NMR (600.1 MHz, CDCl$_3$): δ 5.20 (‘t’, *J* = 4.7, 1H, H-3′), 5.19 (‘t’, *J* = 9.4, 1H, H-3), 5.16 (‘t’, *J* = 3.3, 1H, H-2′), 5.10 (‘t’, *J* = 9.7, 1H, H-4), 5.06 (dd, *J* = 9.8, 8.2, 1H, H-2), 5.04 (d, *J* = 4.2, 1H, H-1′), 4.93 (‘q’, *J* = 5.5, 2.9 1H, H-4′) 4.64 (d, *J* = 7.8, 1H, H-1), 4.30 (dd, *J* = 12.9, 2.5, 1H, H-5a′), 4.27 (dd, *J* = 12.6, 2.4, 1H, H-6a), 4.13 (dd, *J* = 12.6, 2.4, 1H, H-6b), 3.74 (ddd, *J* = 10.2, 5.4, 2.4, 1H, H-5), 3.52 (dd, *J* = 13.2, 3.6, 1H, H-5b′), 2.12 (s, 3H, C(O)CH$_3$), 2.09 (s, 3H, C(O)CH$_3$), 2.07 (s, 3H, C(O)CH$_3$), 2.03 (s, 3H, C(O)CH$_3$), 2.02 (s, 3H, C(O)CH$_3$), 2.01 (s, 3H, C(O)CH$_3$), 2.00 (s, 3H, C(O)CH$_3$); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 170.6 (*C*(O)CH$_3$), 170.2 (*C*(O)CH$_3$), 170.0 (*C*(O)CH$_3$), 169.8 (*C*(O)CH$_3$), 169.5 (*C*(O)CH$_3$), 169.4 (*C*(O)CH$_3$), 168.9 (*C*(O)CH$_3$), 100.9 (C-1), 97.6 (C-1′), 72.5 (C-3), 72.1 (C-5), 71.0 (C-2), 68.4 (C-4′), 68.2 (C-4), 66.5 (C-3′, C-2′), 61.7 (C-6), 59.5 (C-5′), 21.0 (C(O)*C*H$_3$), 20.9 (C(O)*C*H$_3$), 20.8 (C(O)*C*H$_3$), 20.7 (C(O)*C*H$_3$), 20.7 (C(O)*C*H_3), 20.6 (C(O)*C*H_3), 20.6 (C(O)*C*H_3); $^1J_{\text{H-1}',\text{C-1}'} = 167.8$; $^1J_{\text{H-1,C-1}} = 161.6$.

4.9. 2,3,4-Tri-*O*-benzyl-α-L-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (27) and 2,3,4-tri-*O*-benzyl-β-L-lyxopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (28)

Compounds **3**[37] (600 mg, 1.2 mmol) and **16** (360 mg, 0.86 mmol) were dissolved at 0 °C in dry CH_2Cl_2 (4 mL). A solution of $SnCl_4$ (1 M in CH_2Cl_2, 26 μL, 0.026 mmol) was added and the mixture was stirred for 20 h at rt. The mixture was diluted with CH_2Cl_2 (20 mL), washed with satd aq $NaHCO_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 3:1) yielded a 7:1 mixture of **27** and **28** (310 mg, 48%) as a colorless oil. $R_f = 0.35$ (petroleum ether–EtOAc 3:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): **27**: δ 7.36–7.27 (m, 15H, Ph) 5.22 ('t', $J = 9.0$, 1H, H-3), 5.14 (d, $J = 2.4$, 1H, H-1′), 5.10 ('t', $J = 9.0$, 1H, H-4), 5.05 (dd, $J = 10.8$, 9.0, 1H, H-2), 4.80–4.60 (m, 7H, CH_2, H-1), 4.28 (dd, $J = 12.0$, 4.8, 1H, H-6a), 4.11 (dd, $J = 12.0$, 2.4, 1H, H-6b), 4.05–3.99 (m, 1H, H-4′), 3.82 ('t', $J = 2.4$, 1H, H-2′), 3.79 (dd, $J = 11.4$, 6.0, 1H, H-5a′), 3.73–3.67 (m, 1H, H-5), 3.66 (dd, $J = 9.0$, 2.4, 1H, H-3′), 3.39 ('t', $J = 11.4$, 1H, H-5b′), 2.09 (s, 3H, $C(O)CH_3$), 2.03 (s, 3H, $C(O)CH_3$), 2.01 (s, 3H, $C(O)CH_3$), 2.00 (s, 3H, $C(O)CH_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$): **27**: δ 170.7 (*C*(O)CH_3), 170.6 (*C*(O)CH_3), 170.2 (*C*(O)CH_3), 169.4 (*C*(O)CH_3), 138.8 (quaternary C), 138.4 (quaternary C), 138.1 (quaternary C), 128.5–127.5 (aromatic C), 94.5 (C-1′), 94.4 (C-1), 78.6 (C-3′), 74.4 (C-2′), 74.0 (C-4′), 72.6 (C-3), 71.9 (C-5), 70.7 (C-2), 68.3 (C-4), 61.8 (C-5′), 61.7 (C-6), 20.8 (C(O)*C*H_3), 20.7 (C(O)*C*H_3), 20.6 (C(O)*C*H_3), 20.5 (C(O)*C*H_3); $^1J_{\text{H-1}',\text{C-1}'} = 173.2$; $^1J_{\text{H-1,C-1}} = 163.8$; **28**: δ 100.8 (C-1′), 100.7 (C-1); $^1J_{\text{H-1}',\text{C-1}'} = 164.7$; $^1J_{\text{H-1,C-1}} = 162.8$; (MALDI-TOF-MS): m/z 773.4 $[M+Na]^+$, 789.4 $[M+K]^+$; Anal. Calcd for $C_{40}H_{46}O_{14}$: C, 63.99; H, 6.18. Found: C, 63.55; H, 6.04.

4.10. 2,3,4-Tri-*O*-acetyl-α-L-lyxopyranosyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranoside (30)

Compounds **13** (280 mg, 0.66 mmol) and **7**[38] (200 mg, 0.6 mmol) were dissolved at 0 °C in dry CH_2Cl_2 (3 mL). $BF_3\cdot OEt_2$ (8 μL, 0.07 mmol) was added and the mixture was stirred for 2 h at rt. The mixture was diluted with CH_2Cl_2 (20 mL), washed with satd aq $NaHCO_3$ (2 × 20 mL) and with brine (1 × 20 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by FC (petroleum ether–EtOAc 2:1) yielded **30** (255 mg, 72%) as a white solid. $R_f = 0.35$ (petroleum ether–EtOAc 1:1); ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 5.38 (d, $J = 3.6$, 2.4 1H, H-2′), 5.34 (dd, $J = 10.2$, 3.6, 1H, H-3′), 5.27 (dd, $J = 10.2$, 4.8, 1H, H-4′), 5.17 (d, $J = 2.4$, 1H, H-1′), 5.06–5.04 (m, 2H, H-3, H-4), 4.64 (d, $J = 8.4$, 1H, H-1), 4.25 (dd, $J = 12.6$, 4.8, 1H, H-6a), 4,09 (dd, $J = 12.6$, 2.4, 1H, H-6b), 3.97 (dd, $J = 10.2$, 5.4, 1H, H-5a′), 3.71–3.63 (m, 3H, H-2, H-5, H-5b′), 2.15 (s, 3H, $C(O)CH_3$), 2.11 (s, 3H, $C(O)CH_3$), 2.09 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$), 2.02 (s, 3H, $C(O)CH_3$), 2.01 (s, 3H, $C(O)CH_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 170.8 (*C*(O)CH_3), 170.7 (*C*(O)CH_3), 170.6 (*C*(O)CH_3), 170.5 (*C*(O)CH_3), 169.9 (*C*(O)CH_3), 169.8 (*C*(O)CH_3), 95.6 (C-1), 93.9 (C-1′), 72.6 (C-3), 72.1 (C-5), 68.7 (C-2′), 68.2 (C-3′), 67.9 (C-4), 66.0 (C-4′), 63.1 (C-2), 61.4 (C6), 60.4 (C-5′), 21.8 (C(O)*C*H_3), 21.7 (C(O)*C*H_3), 21.6 (C(O)*C*H_3), 21.6 (C(O)*C*H_3), 21.5 (C(O)*C*H_3), 21.5 (C(O)*C*H_3); $^1J_{\text{H-1}',\text{C-1}'} = 176.3$; $^1J_{\text{H-1,C-1}} = 162.7$; (MALDI-TOF-MS): m/z 712.3 $[M+Na]^+$, 628.2 $[M+K]^+$; Anal. Calcd for $C_{23}H_{31}N_3O_{15}$: C, 46.86; H, 5.30; N, 7.13. Found: C, 46.80; H, 5.10; N, 6.79.

4.11. General procedure for the deacetylation of disaccharides 25, 26, and 30

To a solution of the peracetylated disaccharide in MeOH is added a solution of sodium methylate (0.5 M in MeOH, 0.15 equiv). The mixture is stirred for 10–48 h at rt. After neutralization with acidic ion exchanger (DOWEX 50 W X8, H^+ form), the mixture is filtered and lyophilized to yield the deacetylated disaccharide in quantitative yield.

4.12. α-L-Lyxopyranosyl β-D-glucopyranoside (1)

Compound **25** was deacetylated according to the general procedure in Section 4.11. RP-HPLC (semi-preparative column) (5–65% B in 30 min): t_R 3.3 min; ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 5.10 (d, $J = 2.7$, H-1′), 4.52 (d, $J = 7.9$, 1H, H-1), 3.86–3.78 (m, 3H, H-4′, H-5a′, H-6a), 3.75 (dd, $J = 8.7$, 2.7, 1H, H-2′), 3.67–3.59 (m, 3H, H-3′, H-5, H-6b), 3.37 ('t', $J = 8.8$, 1H, H-4), 3.31–3.26 (m, 2H, H-3, H-5b′), 3.21 ('t', J=7.9, 1H, H-2); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 98.7 (C-1), 97.4 (C-1′), 77.8 (C-3), 77.4 (C-4), 74.1 (C-2), 71.8 (C-2′), 70.8 (C-5′), 67.8 (C-4′), 64.1 (C-3′), 64.0 (C5), 62.2 (C6); $^1J_{\text{H-1}',\text{C-1}'} = 174.7$; $^1J_{\text{H-1,C-1}} = 166.6$; (MALDI-TOF-MS): m/z 335.2 $[M+Na]^+$, 341.4 $[M+K]^+$.

4.13. β-L-Lyxopyranosyl β-D-glucopyranoside (29)

Compound **26** was deacetylated according to the general procedure in Section 4.11. RP-HPLC (semi-preparative column) (5–65% B in 30 min): $t_R = 3.2$ min; ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 4.76 (d, $J = 1.7$, H-1′), 4.31 (d, $J = 6$, 1H, H-1), 3.87 (dd, $J = 2.9$, 12.6, 1H, H-5a′), 3.71–2.68 (m, 1H, H-4′), 3.62 (dd, $J = 10.8$, 4.8, 1H, H6a), 3.55–3.42 (m, 3H, H-3′, H-2′, H-6b), 3.12–3.00

(m, 4H, H-2, H-3, H-4, H-5), 3.08 (dd, $J = 12.6, 8.4$, 1H, H-5b′); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 102.3 (C-1), 102.2 (C-1′), 76.8 (C-3), 75.9 (C-4), 73.6 (C-2), 71.6 (C-2′), 79.5 (C-5), 67.7 (C-3′), 67.0 (C-4′), 62.3 (C5′), 60.6 (C6); $^1J_{\text{H-1}',\text{C-1}'} = 162.6$; $^1J_{\text{H-1,C-1}} = 158.4$; (MALDI-TOF-MS): *m*/*z* 335.2 [*M*+Na]$^+$, 341.4 [*M*+K]$^+$.

4.14. α-L-Lyxopyranosyl 2-azido-2-deoxy-β-D-glucopyranoside (31)

Compound **30** was deacetylated according to the general procedure in Section 4.11. RP-HPLC (semi-preparative column) (5–45% B in 30 min): $t_R = 3.3$ min; ^{1}H NMR (600.1 MHz, CDCl$_3$): δ 5.13 (d, $J = 2.4$, H-1′), 4.64 (d, $J = 9.6$, 1H, H-1), 3.87–3.76 (m, 4H, H-2′, H-3′, H-4′, H-6a), 3.74 (dd, $J = 10.2, 4.2$, 1H, H-5a′), 3.63 (dd, $J = 12.0, 4.8$, 1H, H-6b), 3.51 (dd, $J = 10.8, 10.2$, 1H, H-5b′), 3.42–3.30 (m, 4H, H-2, H-3, H-4, H-5); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 96.6 (C-1′), 96.1 (C-1), 76.1 (C-3), 74.0 (C5), 70.3 (C-3′), 69.4 (C-2′), 69.3 (C-4), 66.1 (C-4′), 65.6 (C-2), 72.8 (C-5′), 60.3 (C6); $^1J_{\text{H-1}',\text{C-1}'} = 173.1$; $^1J_{\text{H-1,C-1}} = 166.0$; (MALDI-TOF-MS): *m*/*z* 359.9 [*M*+Na]$^+$, 375.9 [*M*+K]$^+$.

4.15. α-L-Lyxopyranosyl 2-amino-2-deoxy-β-D-glucopyranoside (2)

To a solution of **31** (35 mg, 0.1 mmol) in MeOH (5 mL) was added 10% Pd on carbon catalyst (15 mg), and the mixture was vigorously stirred under a hydrogen atmosphere (1 atm) at rt for 2 h. After filtration and lyophilization, **2** was obtained as a white solid (32 mg, 99%). RP-HPLC (semi-preparative column) (5–45% B in 30 min): $t_R = 3.2$ min; ^{1}H NMR (600.1 MHz, CDCl$_3$): δ 5.10 (d, $J = 3.0$, H-1′), 4.53 (d, $J = 8.4$, 1H, H-1), 3.84–3.72 (m, 5H, H-2′, H-3′, H-4′, H-5a′, H-6a), 3.62 (dd, $J = 12.6, 6.0$, 1H, H-6b), 3.49 (dd, $J = 11.4, 3.0$, 1H, H-5b′), 3.38–3.25 (m, 3H, H-3, H-4, H-5), 2.64 (‘t’, $J = 8.4$, 1H, H-2); ^{13}C NMR (150.9 MHz, CDCl$_3$): δ 97.5 (C-1), 96.5 (C-1′), 76.3 (C5), 75.1 (C-3), 70.2 (C-3′), 69.6 (C-4), 69.4 (C-2′), 66.3 (C-4′), 62.9 (C-5′), 60.6 (C6), 56.1 (C-2); $^1J_{\text{H-1}',\text{C-1}'} = 170.5$; $^1J_{\text{H-1,C-1}} = 161.7$; (MALDI-TOF-MS): *m*/*z* 359.9 [*M* + Na]$^+$, 375.9 [*M*+K]$^+$.

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References

1. Wright, D. E. *Tetrahedron* **1979**, *35*, 1207–1237.
2. Weitnauer, G.; Hauser, G.; Hofmann, C.; Linder, U.; Boll, R.; Pelz, K.; Glaser, S. J.; Bechthold, A. *Chem. Biol.* **2004**, *11*, 1403–1411.
3. Belova, L.; Tenson, T.; Xiong, L.; McNicholas, P. M.; Mankin, A. S. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3726–3731.
4. McNicholas, P. M.; Najarian, D. J.; Mann, P. A.; Hesk, D.; Hare, R. S.; Shaw, K. J.; Black, T. A. *Antimicrob. Agents Chemother.* **2000**, *44*, 1121–1126.
5. McNicholas, P. M.; Mann, P. A.; Najarian, D. J.; Miesel, L.; Hare, R. S.; Black, T. A. *Antimicrob. Agents Chemother.* **2001**, *45*, 79–83.
6. Boll, R.; Hofmann, C.; Heitmann, B.; Hauser, G.; Glaser, S.; Koslowski, T.; Friedrich, T.; Bechthold, A. *J. Biol. Chem.* **2006**, *281*, 14756–14763.
7. Hofmann, C.; Boll, R.; Heitmann, B.; Hauser, G.; Duerr, C.; Frerich, A.; Weitnauer, G.; Glaser, S. J.; Bechthold, A. *Chem. Biol.* **2005**, *12*, 1137–1143.
8. Bredereck, H.; Hoschele, G.; Ruck, K. *Chem. Ber.* **1953**, *86*, 1277–1280.
9. Lemieux, R. U.; Bauer, H. F. *Can. J. Chem.* **1954**, *32*, 340–344.
10. Helferich, B.; Weis, K. *Chem. Ber.* **1956**, *89*, 314–321.
11. Birkofer, L.; Hammes, B. *Justus Liebigs Ann. Chem.* **1973**, 731–739.
12. Bar-Guilloux, E.; Defaye, J.; Driguez, H.; Robic, D. *Carbohydr. Res.* **1975**, *45*, 217–236.
13. Cook, S. J.; Khan, R.; Brown, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 343–348.
14. Kamiya, S.; Esaki, S.; Tanaka, R. *Agric. Biol. Chem.* **1984**, *48*, 2137–2138.
15. Olah, V. A.; Harangi, J.; Liptak, A. *Carbohydr. Res.* **1988**, *174*, 113–120.
16. Nishizawa, M.; Kodama, S.; Yamane, Y.; Kayano, K.; Hatakeyama, S.; Yamada, H. *Chem. Pharm. Bull.* **1994**, *42*, 982–984.
17. Nishizawa, M.; Garcia, D. M.; Noguchi, Y.; Komatsu, K.; Hatakeyama, S.; Yamada, H. *Chem. Pharm. Bull.* **1994**, *42*, 2400–2402.
18. Ronnow, T. E. C. L.; Meldal, M.; Bock, K. *Tetrahedron: Asymmetry* **1994**, *5*, 2109–2122.
19. Rønnow, T. E. C. L.; Meldal, M.; Bock, K. *J. Carbohydr. Chem.* **1995**, *14*, 197–211.
20. Posner, G. H.; Bull, D. S. *Tetrahedron Lett.* **1996**, *37*, 6279–6282.
21. Hiruma, K.; Kajimoto, T.; Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 9265–9270.
22. Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodriguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.
23. Srivastava, V. K.; Schuerch, C. *Tetrahedron Lett.* **1979**, *35*, 3269–3272.
24. Hodosi, G.; Kováč, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335–2336.
25. Pratt, M. R.; Leigh, C. D.; Bertozzi, C. R. *Org. Lett.* **2003**, *5*, 3185–3188.
26. Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.
27. Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Melcher, L. M. *J. Org. Chem.* **1990**, *55*, 5196–5197.
28. Oscarson, S.; Sehgelmeble, F. W. *J. Am. Chem. Soc.* **2000**, *122*, 8869–8872.

29. Green, L. G.; Ley, S. V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 427–448.
30. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.
31. Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155–173.
32. Levy, D. E.; Fügedi, P. *The Organic Chemistry of Sugars*; CRC Press: Boca Raton, 2006.
33. Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471–1491.
34. Klotz, W.; Schmidt, R. R. *J. Carbohydr. Chem.* **1994**, *13*, 1093–1101.
35. Tamura, J.-i. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 177–193.
36. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 180–183.
37. Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249–1256.
38. Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826–1847.
39. Zhang, J.; Kováč, P. *J. Carbohydr. Chem.* **1999**, *18*, 461–469.
40. Watt, G. M.; Flitsch, S. L.; Fey, S.; Elling, L.; Kragl, U. *Tetrahedron: Asymmetry* **2000**, *11*, 621–628.
41. Desmet, T.; Nerinckx, W.; Stals, I.; Callewaert, N.; Contreras, R.; Claeyssens, M. *Anal. Biochem.* **2002**, *307*, 361–367.
42. Bennett, M.; Gill, G. B.; Pattenden, G.; Shuker, A. J.; Stapleton, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 929–937.
43. Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.
44. Gigg, R.; Warren, C. D. *J. Chem. Soc.* **1965**, 2205–2210.
45. Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731–732.
46. Reist, E. J.; Gueffroy, D. E.; Goodman, L. *J. Am. Chem. Soc.* **1964**, *86*, 5658–5663.
47. Bobek, M.; Whistler, R. L. *Methods Carbohydr. Chem.* **1972**, *6*, 292–296.
48. Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.
49. Paulsen, H.; Meinjohanns, E.; Reck, F.; Brockhausen, I. *Liebigs Ann. Chem.* **1993**, 721–735.
50. Weingart, R.; Schmidt, R. R. *Tetrahedron Lett.* **2000**, *41*, 8753–8758.
51. Larsen, K.; Olsen, C. E.; Motawia, M. S. *Carbohydr. Res.* **2008**, *343*, 383–387.
52. Zinner, H.; Brandner, H. *Chem. Ber.* **1956**, *89*, 1507–1515.