Investigations towards the Synthesis of 5-Amino-L-lyxofuranosides and 4-Amino-lyxopyranosides and NMR Analysis

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Abstract The reactivity of trifluoromethanesulfonyl esters derived from L-lyxofuranosides and L-lyxopyranosides was investigated with various 5-aminopyrimidines as nucleophiles with the expectation to synthesize N-substituted 5-amino-ribosugars. The lyxopyranoside forms were found to be unreactive, while the lyxofuranoside forms were found to be reactive with 5-aminopyrimidines, yielding novel N-substituted 5-amino-lyxofuranosides. We report on the synthesis of these novel N-substituted lyxofuranosides and the systematic analyses of NMR data that demonstrate trends within each series: furano-, pyrano-, β- and α-anomers of L-lyxose and β-D-ribopyranoside forms. The data call for caution when identifying these monosaccharides in isomeric mixtures.

Key words L-lyxofuranoses, L-lyxopyranoses, D-ribopyranoses, conformation analysis, heterocycles, NMR spectroscopy

In our research exploring the self-assembly properties of alternative recognition elements such as 5-aminouracil and 2,4,5-triaminopyrimidine substituted-pyrrolidines, it was necessary to develop new N-substituted 4-amino-D-ribofuranose sugars.1–3 We proposed the corresponding L-lyxopyranose derivatives as outlined in Scheme 1 as intermediates en route to the final pyrrolidine compounds. This synthetic approach is based on the fact that nucleophiles can attack the C(4) position of a substituted lyxopyranose sugar (with a good leaving group at the C(4)-position) through a bimolecular nucleophilic substitution (SN2) displacement, resulting in the corresponding ribopyranose framework.4–7 However, the synthesis of N-substituted 4-amino-D-ribopyranose derivatives proved problematic with amino pyrimidine heterocycles, presumably due to the poor nucleophilicity of these alternative amino nucleobases.

For comparison, we also studied the SN2 reaction with the L-lyxofuranosyl series with the awareness that 5-amino-heterocycles may react more readily at a primary carbon. When comparing the results of the L-lyxopyranose and L-lyxofuranose series, we found that there could be some uncertainty in the assignments as α/β anomic mixtures of alcohols derived from L-lyxose when they are actually furanoside/pyranoside mixtures.8 To clarify this issue, we have synthesized, measured NMR spectra and contrasted the chemical shift trends of the furanosyl and pyranosyl L-lyxose series – both from this work and those in the literature – and came to the conclusion that identifying the minor compound in isomeric mixtures of monosaccharides can be crucial and should always rely on accurate identification based on corroborating NMR techniques.
The starting lyxofuranosides 1–3 were obtained in a one-pot reaction, in which protection of the anomeric position and formation of the acetal were accomplished by heating the starting L-lyxose in the presence of acetone and the appropriate alcohol in acidic medium for short periods of time. Characterization of small amounts of impurities that co-eluted with the desired products showed discrepancies with the results described earlier. Instead of mixtures of anomers, we identified trace amounts of pyranose products 5–7. In our hands, we could not find mixtures of anomers in any of the cases. The synthesis of starting materials in the L-lyxopyranose series was accomplished by following existing procedures (Scheme 2).

L-Lyxopyranosides 5–7 were prepared in a stepwise fashion. First, protection of the anomeric position by a regular Fischer glycosidation was conducted with corresponding anhydrous alcohol in the presence of an acid. The reaction produced, what we originally thought to be, anomeric mixtures of (misassigned) anomers. It is noticeable that alcohols of mixtures of furanose forms, which was difficult to purify. Detailed analysis by NMR (see Figure S.54 in the Supporting Information) showed that alcohols 5 and 6 indeed contained small amounts of furanose forms (1 and 2, respectively), instead of mixtures of anomers.

The trifluoromethane sulfonate esters of alcohols (at C4 position for the pyranose and C5 position for the furanose series) were generated with trifluoromethanesulfonic anhydride in the presence of DMAP and pyridine at 0 °C. Reactions were quenched by aqueous work-up upon consumption of starting material. The subsequent S_N2 reaction was conducted on the crude triflate intermediates.

**Scheme 2**  
Synthesis of the ketal-protected β-furanosides and α-pyranosides of L-lyxose. Reagents and conditions: (a) Acetone, ROH, H_2SO_4, 60 °C, 4 h (1: 72% and 5: <5%; 2: 48% and 6: <5%; 3: 37% and 7: <5%); (b) ROH, reflux, H^+; 3 h; (c) HCl, acetone, DMP, r.t., 16 h (yields after two steps: 5: 36% and 1: 2<0%; 6: 41% and 2: <10%; 7: 30% and 3: <5%).
The use of cycles and the speed of the reaction led to higher product temperature (probably increasing the solubility of the hetero-

1t–3t and 5t–7t (no purification was attempted due to their instability). The corresponding mesylate leaving groups were not used because they did not react even with sodium azide; whereas the triflate intermediates promptly reacted with the latter nucleophile (Scheme 3 and Table 1, entries 1 and 2). Reaction of the triflate of 1 with 10 over three days at room temperature led to poor yields (entry 3). The use of 3.0 equivalents of heterocycles 10 and 11 and higher temperature (probably increasing the solubility of the heterocycles and the speed of the reaction) led to higher product yields. The use of N,N-bis(trimethylsilyl)acetamide (BSA) increased the solubility of 5-aminouracil 10 and resulted in further improvement of product yields (entry 5), but did not help in the case of 11 (entry 7).

Reactions of triflates with different nucleophiles at 70 °C for up to two days generated by-products resulting from the hydrolysis or decomposition of the starting materials. In the β-L-lyxofuranose series, 2,4,5-triaminopyrimidine 11 produced higher yields than 5-aminouracil 10 when reacting with the 1t–3t triflates, perhaps reflecting the higher nucleophilicity of the 5-NH$_2$ group in 11. For comparison, 5-aminolyxofuranose 18 was synthesized by hydrogenation of azide 12a (see Scheme 5).

Analyses of the NMR spectra of amines 12c–d, 13c–d and 14d, obtained through S$_2$2 reaction with the corresponding trifluoromethanesulphonates, showed similar features when compared with the corresponding alcohols 1–3, respectively (Table 2) and with amine 18. As expected, the electronic nature of the substituents affected the $^1$H and $^{13}$C NMR shift values; that is, substitution of the hydroxy at C(5) with an amino group produced an upfield shift of 20 ppm in the $^{13}$C NMR spectra and up to 0.6 ppm in the $^1$H NMR spectra (Table 2 and Table 3, entries 1 and 5). NOESY NMR spectra of the products of the S$_2$2 reaction confirmed the β-L-lyxofuranosyl form of the compounds. Figure 2 illustrates the NMR spectrum of compound 12c.

<table>
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$^a$Yields determined after isolation and purification by column chromatography; $^b$- indicates no reaction.

$^b$ Starting material 5 was utilized as a mixture of isomers (mixed with 1).

$^c$ By-product 12a was isolated (ca. 5%) by column chromatography.

Effect (nOe) correlations between the proton at the anomeric position with protons at the C(2) and C(4) positions confirmed the expected β-form, in agreement with the starting materials and the anomeric effect. This was consistent with the NOESY spectra of the alcohol starting materials.

Table 1 Reaction Conditions and Products Obtained from the S$_2$2 Reaction Outlined in Scheme 3

![Scheme 3](image-url)
In the α-L-lyxopyranosyl series, only NaN₃ and BnNH₂ (Table 1, entries 2 and 15) were successful in reacting with triflate 5t, resulting in inversion of configuration at the C(4) position by nucleophilic substitution giving D-ribopyranose derivatives 15a and 15b, respectively. When reactions were run with heterocycles 10 and 11, degradation of triflate 5t was mostly observed, with only very small amounts of the substituted products being isolated; this reflects the poor nucleophilicity of heterocycles 10 and 11. Analysis of the resulting compounds revealed that the reaction products (expected 15c and 15d) had the β-L-lyxofuranose form instead of the anticipated β-D-ribopyranose form. NMR comparisons with prepared furanoses showed that these reaction products were the same as 12c and 12d. Both pyranose and furanose triflates reacted with good nucleophiles such as azide 8 and benzylamine 9 (Scheme 4) in S₂N² reactions. Therefore, in these cases, while the isolated major product was the pyranosyl derivative, a minor (furanosyl) product was isolated in small yields or, in some cases, ‘lost’ during the purification procedures. However, regarding the reac-

<table>
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<th>H-3</th>
<th>H-4</th>
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<td>74.5</td>
<td>66.5</td>
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*Lf = β-L-lyxofuranoside; Lp = α-L-lyxopyranoside.

For comparison, compound 19 was made by hydrogenolysis of 3 (see Scheme 5).

U = 5-uracil.

Py = 5-(2,4-diamino)pyrimidine.

Assignments may be interchanged.
tion of pyrimidines 10 and 11 with 5t (mixed with its iso-
mer), it seemed that the minor compound (the furanose
form, 1t) is the only isomer able to react with poor nucleo-
philes (Table 1, entries 11 and 13), whereas the pyranose
form 5t is not reactive with 10 and 11. When Sn2 reactions
were repeated starting with pure pyranoses 5–7 and nu-
cleophiles 10 and 11, the expected ribopyranoses 15c/d,
16c/d, and 17c/d were not formed (Table 1, entries 12, 14,
16–19), confirming our previous results that only the fura-
nose forms undergo reaction.

We attempted an alternative synthesis of 15c as depict-
ed in Scheme 5. It is known that 5-bromouracil can act as
an electrophile and be attacked by amines under different
reaction conditions (heat without solvent,14–16 reflux, 16–18
or microwave19). Therefore, we prepared aminosugar 20
and reacted it with 5-bromouracil. Unfortunately, this ‘in-
verse approach’ in DMF did not generate the expected com-
 pound (15c), but rather led to the N-formylated sugar deriv-
ative 21. We did not explore this pathway further, but sus-
pect that the 5-bromouracil assisted in the formylation
process. Heterocycle-assisted N-formylation reactions un-
der mild conditions have been described utilizing imidazole
with primary amines.20 Full characterization of 21 revealed
the NMR trends to be consistent with the rest of the
β-D-ribopyranose compounds and was comparable to com-
 pound 22 prepared via a different route.

To address the question of dealing with mixtures of ano-
ers versus mixtures of furanoses and pyranoses,8 we scru-
tinized the 1H and 13C NMR data of our compounds to find
trends in chemical shifts, supported by other NMR spectro-
scopic techniques that would prove useful in assigning the
structures. Table 2 and Table 3 summarize the full charac-

Scheme 4 Reaction scheme for the mixture of isomers of 5 and subsequent Sn2 reactions with nucleophiles

Scheme 5 Generation of the amines 18 and 20 for the ‘inverse approach’ in which the sugar acts as the nucleophile with a leaving group on the heterocycle. Attempted synthesis of 15c. Synthesis of 19 and 22 are shown for comparison. Reagents and conditions: (a) H2, Pd/C (5%), MeOH, r.t., 6 h (18: 95%; 20: 95%); (b) H2, Pd(OH)2, MeOH, r.t., 20 h (98%); (c) 5-bromouracil, DMF, 70 °C, 16 h (21: 56% and 15c: not found); (d) BzCl, DIPEA, CH2Cl2, r.t., 16 h (82%).
terization of the sugar derivatives that we have obtained, documenting trends within and between the furanose and pyranose series. Extensive NMR measurements were conducted using the same deuterated solvent (DMSO-\(d_6\)) system both for the already published products and related compounds originally reported in CDCl\(_3\) (Table 2), and for the heterocycle-attached furanose compounds, which are insoluble in CDCl\(_3\) (Table 3). Analyses were carried out by HSQC and COSY NMR spectroscopy of all the structures, in addition to NOESY spectroscopy to confirm the configuration of the pyran or furan rings and the configuration in the anomeric position (see Figure 3 and the Supporting Information); HMBC spectroscopy was used to corroborate the configuration of the rings (see Figure 2 and the Supporting Information) of some of the starting materials and several products.

In general, the trends in chemical shift for pyranosides versus furanosides (within a sugar series) are consistent, and independent of solvent and substituents in the anomeric position. For example, in \(^1\)H NMR spectra for the lyxo series, all shifts except for the C(5)H both for the lyxo and the ribo series, as documented in Table 2 (entries 1–3 and entries 11 and 12) and Table 3 (entries 1–3 and entries 6 and 7).

There is also a consistent trend for the different anomers within a given series. The signals for the anomeric position for \(\beta\)-L-lyxofuranosyl compounds appear around 4.8–5.0 ppm in \(^1\)H NMR spectra and 104–107 ppm in \(^13\)C NMR spectra; whereas the corresponding values for the \(\alpha\)-L-lyxo-pyranosyl forms are consistently more upfield: around 4.6–4.8 ppm in the \(^1\)H NMR spectra and below 100 ppm in the \(^13\)C NMR spectra (Table 2, entries 1–8; Table 3). The substitution of the hydroxyl in the C(5) position by an amine in the furanose series up-shifted the CH\(_2\) signal by 20 ppm in the \(^13\)C NMR spectra and by around 0.6 ppm in the \(^1\)H NMR spectra (Table 2, entries 1–4 versus 5–10). In the ribopyranose series, substitution in position C(4) affected the chemical shift values of position C(4) and C(5) depending on the nature of the substituent, as evidenced in Table 3, entries 10 vs. 12 and 13 and entries 10 vs. 11, respectively.

Thus, caution must be exercised to determine whether the compounds are mixtures of furanose/pyranose (in the ribo- or lyxo-series) versus mixtures of anomers (in the ribo- and lyxo-series). Further NMR spectroscopic (e.g.,
HMBC and NOESY) studies need to be performed to confirm the α- or β- versus furanose- or pyranose-configuration of the sugars at hand.

In conclusion, in our attempts to synthesize N-substituted 5-amino-lyxopyranoside derivatives, we have demonstrated that only the 5-O-trifluoromethanolsulfonate l-lyxofuranoside derivative reacts with 5-aminoericin and 2,4,5-triaminopyrimidine as nucleophiles; S2,2 reactions with 4-O-triflate l-lyxopyranoside derivatives with these heterocyclic nucleophiles were unsuccessful. A detailed NMR spectroscopic characterization of both the starting materials and products enabled us to identify trends in chemical shifts for the corresponding lysosides and ribosides (in the pyran and furano series versus the α- and β-anomers). Identifying trends on chemical shifts within each series and also exceptions between them, will be of utility in future investigations. These exceptions point out the potential pitfalls in attempting to recognize mixtures of anomers versus mixtures of furanosides/pyranosides based on trends in chemical shifts alone.

All reagents were obtained from commercial sources and used without purification. Anhydrous solvents were purchased from EMD Chemicals. All experiments were performed under a nitrogen or argon atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 Å F254 from Angela Technologies, and visualized under a vonious atmosphere. Thin-layer chromatography (TLC) was performed on silica gel 60 Å with particle size 35–70 μm purchased from Acros Organics. NMR spectra were recorded at 20 °C with a Bruker DRX-600. AV-600 (600 MHz for 1H and 150 MHz for 13C) or an AV-400 (400 MHz for 1H and 100 MHz for 13C). Chemical shifts (δ) are given in parts per million (ppm). 1H and 13C chemical shifts in CDC13 were referenced to tetramethylsilane (TMS) δ 0 ppm and 77.16 ppm, respectively. 1H and 13C chemical shifts in DMSO-d6 were referenced to dimethyl sulfoxide (DMSO) δ 39.52 ppm, respectively. NMR peak assignments were made based on COSY, HSQC and/or NOESY 2D experiments. Mass spectra were measured with an Agilent ESI-TOF or a ThermoElectron Finnigan LTQ ion trap mass spectrometer.

Synthesis of the Protected Furanoside Sugars

The protection of the furanoside sugars was developed by following the procedure described by Coleman et al.21 L-Lyxose (1.20 g, 8.00 equiv.) was stirred at reflux until disappearance of the starting material, as monitored by TLC (3–5 h, depending on the alcohol). The reaction was quenched with saturated aq. NaHCO3 solution and the aqueous solution was extracted three times with EtOAc. The combined organic layers were dried with anhydrous Na2SO4, filtered and evaporated to dryness. Analysis of the crude material by 1H NMR spectroscopy showed mixtures of furanose and pyranose products up to 1:0.10 ratio (depending on the reaction). The crude reaction mixture was subjected to column chromatography to afford the corresponding protected lyxofuranoside. Traces (>5%) of the corresponding 2,3-O-isopropylidene-α-L-lyxopyranoside were found in the crude material in all cases.

Methyl 2,3-O-Isopropylidene-β-L-lyxofuranoside (1)22 Yield: 1.17 g (72%); oil; Rf (hexanes/EtOAc, 8:2) = 0.18.

1 H NMR (400 MHz, CDCl3): δ = 4.92 (s, 1 H, H-1), 4.74–4.78 (m, 1 H, H-3), 1.29 (s, 3 H, CH3), 4.56 (d, J = 5.9 Hz, 1 H, H-2), 4.01–4.06 (m, 1 H, H-4), 3.87–3.97 (m, 2 H, H-5a, H-5b), 3.32 (s, 3 H, OCH3), 2.42 (br s, 1 H, OH), 1.45 (s, 3 H, CH3).

1 3C NMR (100 MHz, CDCl3): δ = 112.8 (C(CH3)2), 107.2 (C-1, C-10), 80.4 (C-3), 85.3 (C-2), 79.4 (C-4), 61.2 (C-5), 54.8 (OCH3), 26.0 (C(CH3)3), 24.7 (CCH3).

ESI(+)-MS: m/z calcd. for C9H17O5 [M + H]+: 205.11; found: 205.11.

Data in agreement with the literature22 (ent-1).

Allyl 2,3-O-Isopropylidene-β-L-lyxofuranoside (2)8 Yield: 884 mg (48%); oil; Rf (hexanes/EtOAc, 8:2) = 0.25.

1 H NMR (600 MHz, CDCl3): δ = 5.81 (dddd, J = 17.5, 10.4, 6.4, 5.5 Hz, 1 H, CH=CH2), 5.21 (d, J = 17.2 Hz, 1 H, CH=CH-trans), 5.12 (d, J = 10.4 Hz, 1 H, CH=CH-cis), 5.02 (s, 1 H, H-1), 4.72 (dd, J = 5.7, 4.3 Hz, 1 H, H-3), 4.57 (d, J = 5.7 Hz, 1 H, H-2), 4.09 (dd, J = 12.3, 5.5 Hz, 1 H, OHCHCH=CH2), 4.03 (dd, J = 9.4, 5.1 Hz, 1 H, H-4), 3.90 (dd, J = 12.3, 6.4 Hz, 1 H, OHCHCH=CH2), 3.81–3.87 (m, 2 H, H-5a, H-5b), 2.75 (br s, 1 H, OH), 1.39 (s, 3 H, CH3), 1.24 (s, 3 H, CH3).

13C NMR (150 MHz, CDCl3): δ = 133.7 (CH=CH2), 117.4 (CH=CH2), 112.5 (C(CH3)2), 105.1 (C-1), 85.0 (C-2), 80.0 (C-3), 79.5 (C-4), 67.7 (OCH3=CH2), 60.7 (C-5), 25.7 (CCH3), 24.4 (CCH3).

1 H NMR (600 MHz, DMSO-d6): δ = 5.89 (dddd, J = 16.2, 10.8, 5.9, 5.0 Hz, 1 H, CH=CH2), 5.25 (d, J = 17.3, 1.7 Hz, 1 H, CH=CH-trans), 5.12 (d, J = 10.4, 1.6 Hz, 1 H, CH=CH-cis), 4.95 (s, 1 H, H-1), 4.70–4.75 (m, 2 H, H-3, OH), 4.53 (d, J = 5.5 Hz, 1 H, H-2), 4.09 (dd, J = 13.3, 5.0 Hz, 1 H, OHCHCH=CH2), 3.94 (dd, J = 13.3, 5.1 Hz, 1 H, OHCH=CH2), 3.88–3.92 (m, 1 H, H-4), 3.84 (dt, J = 11.2, 5.6 Hz, 1 H, H-5b), 3.51–3.57 (m, 1 H, H-5a), 1.34 (s, 3 H, CH3), 1.24 (s, 3 H, CH3).

13C NMR (150 MHz, DMSO-d6): δ = 134.6 (CH=CH2), 116.7 (CH=CH2), 111.4 (C(CH3)2), 104.8 (C-1), 84.4 (C-2), 80.7 (C-3), 79.1 (C-4), 67.1 (OCH3=CH2), 58.9 (C-5), 26.0 (CCH3), 24.7 (CCH3).

ESI(+)-MS: m/z calcd. for C9H17O5 [M + H]+: 231.12; found: 231.12.

Data in agreement with the literature.8

Benzyl 2,3-O-Isopropylidene-β-1-lyxofuranoside (3)3 Yield: 828 mg (37%); yellow oil; Rf (hexanes/EtOAc, 9:1) = 0.10.

1 H NMR (600 MHz, CDCl3): δ = 7.28–7.37 (m, 5 H, 5-Hn), 5.15 (s, 1 H, H-1), 4.81 (dd, J = 5.6, 3.8 Hz, 1 H, H-3), 4.66–4.71 (m, 2 H, CH2PH, H-2), 4.50 (d, J = 11.7 Hz, 1 H, CHPhH), 4.11–4.15 (m, 1 H, H-4), 4.00 (dd, J = 11.5, 4.9 Hz, 1 H, H-5b), 3.94 (dd, J = 11.7, 4.5 Hz, 1 H, H-5a), 1.82 (br s, 1 H, OH), 1.47 (s, 3 H, CH3).

Data in agreement with the literature.8
Synthesis of the Protected Pyranose Sugars 4b and 4c

L-Lyxose (1.5 g, 10 mmol, 1 equiv) was dissolved in the corresponding freshly distilled alcohol (allyl or benzyl alcohol, 100 mmol, 10 equiv). The solution was immersed in an ice bath and H2SO4 (6.1 mol%) was added dropwise. The solution was warmed to r.t., heated to reflux for 3 h and stirred overnight at r.t. Reaction progress was monitored by TLC (90:10, CH2Cl2/MeOH) and the reaction was quenched with Amberlyst A-26(OH) resin (2 g). The mixture was shaken for 30 min, filtered, and the resin was washed with MeOH. The combined filtrate and washings were evaporated and the residue was washed several times with diethyl ether (30 mL each) to remove the excess alcohol. The residue was subjected to column chromatography (CH2Cl2/MeOH, 9:1 and hexanes/EtOAc, 2:8, respectively) to afford products 4b and 4c, respectively.

Allyl α-1-Lyxopyranoside (4b)10

Yield: 1.34 g (71%); white amorphous solid; Rf (CH2Cl2/MeOH, 9:1) = 0.40.

1H NMR (600 MHz, DMSO-d6): δ = 5.88 (dddd, J = 17.1, 10.4, 5.6, 4.8 Hz, 1 H, CH=CH2), 5.25 (d, J = 17.1 Hz, 1 H, CH=CH2-trans), 5.14 (d, J = 10.4 Hz, 1 H, CH=CH2-cis), 4.76–4.81 (m, 2 H, 2 × OH), 4.65 (d, J = 5.5 Hz, 1 H, OH), 4.56 (d, J = 2.8 Hz, 1 H, H-1), 4.09 (dd, J = 13.3, 4.8 Hz, 1 H, OCHCH=CH2), 3.91 (dd, J = 13.3, 5.6 Hz, 1 H, OCHCH=CH2), 3.55–3.61 (m, 2 H, H-2, H-4), 3.49 (dd, J = 10.8, 4.9 Hz, 1 H, H-5b), 3.44–3.47 (m, 1 H, H-3), 3.26 (dd, J = 10.8, 9.4 Hz, 1 H, H-5a).

13C NMR (150 MHz, DMSO-d6): δ = 109.7 (C(CH2)3), 99.9 (C-1), 74.2 (C-3), 74.4 (C-2), 67.3 (C-4), 63.3 (C-5), 56.0 (OCH2), 27.6 (CCH3), 25.7 (CCH2).
1H NMR (400 MHz, DMSO-d6): δ = 5.18 (d, J = 5.4 Hz, 1 H, OH), 4.59 (d, J = 1.9 Hz, 1 H, H-1), 3.90–3.97 (m, 2 H, H-3, H-2), 3.54–3.62 (m, 1 H, H-4), 3.45 (dd, J = 11.5, 4.4 Hz, 1 H, H-5b), 3.35–3.40 (m, 1 H, H-5a), 3.31 (s, 3 H, OCH3), 1.47 (s, 3 H, CH3), 1.27 (s, 3 H, CH3).

13C NMR (100 MHz, DMSO-d6): δ = 108.2 (C(CH3)2), 99.5 (C-1), 77.6 (C-3 or C-2), 74.5 (C-2 or C-3), 66.5 (C-4), 62.0 (C-5), 54.9 (OCH3), 28.0 (CCH3), 26.2 (CCH3).

Data in agreement with the literature6,7,10 (ent-5).

Allyl 2,3-O-Isopropylidene-α-β-lyxopyranoside (6)4,6,10

Yield: 655 mg (57%); yellow oil; Rf (hexanes/EtOAc, 1:1) = 0.70.

1H NMR (600 MHz, CDCl3): δ = 5.87 (ddt, J = 16.3, 10.4, 1.2 Hz, 1 H, CH=CH2), 5.29 (dd, J = 16.3, 1.4 Hz, 1 H, CH=CH2-trans), 5.20 (d, J = 10.4 Hz, 1 H, CH=CH2-cis), 4.76–4.79 (m, 1 H, H-1), 4.25 (dd, J = 12.8, 5.3, 1.2 Hz, 1 H, H-2), 4.12–4.15 (m, 1 H, H-2), 4.05 (dd, J = 12.8, 6.2, 1.2 Hz, 1 H, OCH2CH=CH2), 3.78–3.83 (m, 1 H, H-4), 3.75 (dd, J = 11.6, 3.8 Hz, 1 H, H-5b), 3.67 (dd, J = 11.6, 5.9 Hz, 1 H, H-5a), 3.38–3.44 (m, 1 H, OH), 1.47 (s, 3 H, CH3), 1.32 (s, 3 H, CH3).

13C NMR (150 MHz, CDCl3): δ = 133.5 (CH=CH2), 118.0 (CH=CH2), 109.5 (C(CH3)2), 97.8 (C-1), 76.7 (C-2), 74.6 (C-3), 68.8 (OCH2CH=CH2), 67.4 (C-4), 62.9 (C-5), 27.7 (CCH3), 25.7 (CCH3).

ESI(+)–MS: m/z calcd for C11H18O5Na [M + Na]⁺: 253.10; found: 253.10.

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Methyl 5-Azido-5-deoxy-2,3-O-isopropylidene-β-L-lyxofuranoside (12a)

Yield: 172 mg (overall yield 75%); oil; Rf (hexanes/EtOAc, 9:1) = 0.58.

1H NMR (600 MHz, CDCl3): δ = 4.91 (s, 1 H, H-1), 4.70 (dd, J = 5.9, 3.7 Hz, 1 H, H-3), 4.57 (dt, J = 5.9 Hz, 1 H, H-2), 4.08 (dd, J = 7.6, 5.2, 3.9 Hz, 1 H, H-4), 3.57 (dt, J = 12.8, 6.4 Hz, 1 H, H-5b), 3.47–3.52 (m, 1 H, H-5a), 3.34 (s, 1 H, OCH3), 1.46 (s, 3 H, CH3), 1.31 (s, 1 H, CH3).

13C NMR (150 MHz, CDCl3): δ = 111.9 (C(CH3)2), 106.2 (C-1), 84.0 (C-2), 78.6 (C-3), 77.3 (C-4), 53.7 (OCH3), 48.7 (C-5), 25.0 (CCH3).

ESI(+)–MS: m/z calcd. for C11H19O5Na [M + Na]⁺: 252.10; found: 252.10.

Methyl 4-Azido-4-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (15a)6,24

Yield: 156 mg (overall yield 68%); oil; Rf (hexanes/EtOAc, 9:1) = 0.56.

1H NMR (600 MHz, CDCl3): δ = 4.48–4.52 (m, 1 H, H-3), 4.47 (d, J = 3.8 Hz, 1 H, H-1), 4.00 (dd, J = 6.3, 3.8 Hz, 1 H, H-2), 3.78–3.84 (m, 2 H, CH2H5b), 3.69–3.74 (m, 1 H, H-5a), 3.41 (s, 3 H, OCH3), 1.53 (s, 3 H, CH3), 1.35 (s, 3 H, CH3).

13C NMR (150 MHz, CDCl3): δ = 110.8 (C(CH3)2), 100.9 (C-1), 75.3 (C-2), 72.9 (C-3), 60.2 (C-5), 56.4 (OCH3), 54.9 (C-4), 26.9 (CCH3), 25.6 (CCH3).

ESI(+)–MS: m/z calcd. for C11H19O5Na [M + H]⁺: 230.11; found: 230.11.

ESI(+)–MS: m/z calcd. for C11H19O5Na [M + Na]⁺: 252.10; found: 252.10.

General Procedure for the Sn2 Reaction; Method A

The crude trifluoromethanesulfonate intermediate (1.00 mmol) was dissolved in freshly distilled DMF (10 mL), then the corresponding nucleophile (8 or 9, 3.00 mmol) was added. The suspension was stirred at r.t. overnight, then the reaction mixture was evaporated to dryness. The residue was dissolved in a mixture of CH2Cl2 and water. The organic layer was separated and washed with water and brine, dried with anhydrous MgSO4 filtered and evaporated to obtain an oily residue, which, on purification by silica gel flash chromatography, afforded the expected product.

Methyl 4-Benzylamino-4-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (15b)

Yield: 184 mg (overall yield 63%); oil; Rf (hexanes/EtOAc, 13:7) = 0.66.

1H NMR (600 MHz, CDCl3): δ = 7.28–7.36 (m, 4 H, H-Bn), 7.22–7.27 (m, 1 H, H-3), 4.66 (dd, J = 5.4, 3.8 Hz, 1 H, H-1), 4.33 (d, J = 5.3 Hz, 1 H, H-1), 3.88–3.92 (m, 2 H, NCH2Ph, H-2), 3.81–3.87 (m, 2 H, 5 H, NCH2Ph, H2), 3.45 (s, 3 H, OCH3), 3.37–3.43 (m, 1 H, H-5a), 3.15 (dd, J = 11.0, 6.6, 3.6 Hz, 1 H, H-4), 1.25 (s, 3 H, CH3), 1.23 (s, 3 H, CH3).

13C NMR (150 MHz, CDCl3): δ = 140.2 (C-Bn), 128.5 (C-Bn), 128.1 (C-Bn), 127.2 (C-Bn), 109.7 (C(CH3)2), 102.4 (C-1), 75.8 (C-2), 72.9 (C-3), 63.5 (C-5), 56.6 (OCH3), 52.1 (C-4), 51.1 (PhCH2NH), 27.6 (CCH3), 25.8 (CCH3).
**General Procedure for the S$_2$N$_2$ Reaction; Method B**

The crude trifluoromethanesulfonate intermediate (1.00 mmol) was dissolved in distilled DMF (10 mL), then the corresponding nucleophile (10 or 11, 3.00 mmol) was added. The suspension was stirred at 70 °C until consumption of the starting material was observed (reaction monitored by TLC), then the reaction mixture was evaporated to dryness. The residue was filtered through a pad of Celite® and silica. The pad was washed several times with EtOAc/MeOH (9:1) to avoid dissolving the excess of nucleobase that did not react during the reaction. The filtrate and washes were combined and evaporated. The residue was purified by silica gel flash chromatography to afford the expected product.

**Methyl 5-Deoxy-2,3-isopropylidene-5-(uracil-5-ylamino)-β-l-lyxofuranoside (12c)**

Yield: 147 mg (overall yield 47%); yellow amorphous solid; $R_f$ (EtOAc/MeOH, 9:1) = 0.66.

**ESI(+)-HRMS:** $m/z$ calcd for C$_{13}$H$_{21}$(CH$_2$)$_2$O$_6$N$_3$: 336.1166; found: 334.1486.

**1H NMR** (600 MHz, DMSO-$d_6$): $\delta$ = 11.16 (s, 1 H, NH-uracil), 10.18 (s, 1 H, NH-uracil), 6.47 (dd, $J$ = 3.4 Hz, 1 H, CH-uracil), 4.83 (s, 1 H, H-1), 4.71–4.74 (m, 1 H, H-3), 4.51 (d, $J$ = 5.9 Hz, 1 H, H-2), 4.21–4.23 (m, 1 H, NHCH$_3$), 4.00–4.03 (m, 1 H, H-4), 3.21 (s, 3 H, OCH$_3$), 3.16–3.19 (m, 1 H, H-5a), 3.05–3.12 (m, 1 H, H-5b), 1.37 (s, 3 H, CC$_3$), 1.25 (s, 3 H, CCH$_3$).

**13C NMR** (150 MHz, DMSO-$d_6$): $\delta$ = 168.9 (C-1), 119.0 (C-2), 79.8 (C-3), 77.8 (C-4), 68.8 (OCH$_3$), 42.8 (C-5), 26.0 (CCH$_3$), 24.7 (C$_3$).

**ESI(–)-HRMS:** $m/z$ calcd for C$_{13}$H$_{22}$(CH$_2$)$_2$O$_6$N$_3$: 314.1347; found: 312.1666.

**Allyl 5-Deoxy-2,3-O-isopropylidene-5-(uracil-5-ylamino)-β-l-lyxofuranoside (13c)**

Yield: 174 mg (overall yield 56%); brown-orange amorphous solid; $R_f$ (CH$_2$Cl$_2$/MeOH, 9:1) = 0.22; $R_f$ (CH$_3$CH$_2$OH/MeOH, 9:1) = 0.21. 

**ESI(–)-HRMS:** $m/z$ calcd for C$_{13}$H$_{22}$(CH$_2$)$_2$O$_6$N$_3$: 334.1486; found: 334.1485.

**Benzyl 5-Deoxy-2,3-O-isopropylidene-5-(uracil-5-ylamino)-β-l-lyxofuranoside (14c)**

Yield: 162 mg (overall yield 48%); brown-orange solid; mp 146–148 °C; $R_f$ (CH$_2$Cl$_2$/MeOH, 9:1) = 0.23; $R_f$ (CH$_3$CH$_2$OH/MeOH, 9:1) = 0.20.

**ESI(–)-HRMS:** $m/z$ calcd for C$_{13}$H$_{22}$(CH$_2$)$_2$O$_6$N$_3$: 362.1328; found: 362.1325.
ESI(+) -HRMS: m/z calcd. for C_{10}H_{17}N_{2}O_{5} [M + H]^+: 387.1907; found: 387.1911.

ESI(+) -HRMS: m/z calcd. for C_{10}H_{15}NaO_{5} [M + Na]^+: 409.1726; found: 409.1736.

**General Procedure for the Reduction of the Azides**
Pd/C (5% w/w) (100 mg) was added to the corresponding azide (230 mg, 1.00 mmol) in anhydrous MeOH (5 mL) and the reaction mixture was stirred under an atmosphere of hydrogen (1 atm) until completion of the reaction as monitored by TLC (hexanes/EtOAc, 9:1). The reaction mixture was filtered over a pad of Celite® and evaporated. The product was sufficiently pure to be used without any further purification.

**Methyl 5-Amino-5-deoxy-2,3-O-isopropylidene-β-D-lyxofuranoside (18)**

**Yield:** 193 mg (95%); white amorphous solid; R_f (CHCl_3/MeOH, 95:5) = 0.25.

1H NMR (600 MHz, CDC_3): δ = 4.89 (s, 1 H, H-1), 4.72 (dd, J = 5.8, 3.9 Hz, 1 H, H-3), 4.56 (d, J = 5.8 Hz, 1 H, H-2), 3.92–3.96 (m, 1 H, H-4). 3.32 (s, 3 H, OCH_3) 2.99–3.09 (m, 2 H, H-5a, H-5b), 1.45 (s, 1 H, CHCH_3), 1.30 (s, 3 H, CH(CH_3)_2).

13C NMR (150 MHz, DMSO-d_6): δ = 112.7 (C(CH_3)_2), 107.1 (C-1), 85.2 (C-2), 80.7 (C-3), 80.1 (C-4), 54.6 (OCH_3), 40.9 (C-5), 26.1 (CHCH_3), 24.8 (CH(CH_3)_2).

1H NMR (600 MHz, DMSO-d_6): δ = 4.92 (s, 1 H, H-1), 4.79 (dd, J = 5.9, 3.8 Hz, 1 H, H-3), 4.57 (d, J = 5.9 Hz, 1 H, H-2), 4.07–4.13 (m, 1 H, H-4), 3.27 (s, 3 H, OCH_3), 3.15 (dd, J = 13.3, 3.3 Hz, 1 H, H-5’), 2.92 (dd, J = 13.3, 9.0 Hz, 1 H, H-5). 1.37 (s, 1 H, CHCH_3), 1.26 (s, 3 H, CH(CH_3)_2).

13C NMR (151 MHz, DMSO-d_6): δ = 112.0 (C(CH_3)_2), 106.2 (C-1), 85.4 (C-2), 79.1 (C-3), 75.8 (C-4), 54.1 (OCH_3), 38.0 (C-5), 25.8 (CHCH_3), 24.5 (CH(CH_3)_2).

ESI(+) -HRMS: m/z calcd. for C_{10}H_{18}NO_5 [M + H]^+: 204.1230; found: 204.1221.

**Methyl 4-Amino-4-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (20)**

**Yield:** 193 mg (95%); white amorphous solid; R_f (CHCl_3/MeOH, 95:5) = 0.25.

1H NMR (600 MHz, CDC_3): δ = 4.37 (dd, J = 5.3, 3.9 Hz, 1 H, H-1), 4.34 (d, J = 4.9 Hz, 1 H, H-3), 3.94 (dd, J = 13.2, 8.0 Hz, 1 H, H-2), 3.71 (dd, J = 10.5, 5.7 Hz, 1 H, H-5b), 3.46 (s, 3 H, OCH_3) 3.41–3.45 (m, 1 H, H-5a), 3.18–3.24 (m, 1 H, H-4), 1.53 (s, 3 H, CHCH_3), 1.37 (s, 3 H, CH(CH_3)_2).

13C NMR (150 MHz, DMSO-d_6): δ = 109.9 (C(CH_3)_2), 101.9 (C-1), 75.7 (C-2), 74.5 (C-3), 65.1 (C-5), 56.4 (OCH_3), 49.9 (C-4), 27.5 (CHCH_3), 25.6 (CH(CH_3)_2).

ESI(+) -HRMS: m/z calcd. for C_{10}H_{17}NO_5 [M + H]^+: 204.1230; found: 204.1224.

Data in agreement with the literature.4,6,7

**2,3-O-Isopropylidene-β-D-lyxofuranose (19)**

A suspension of the benzyl protected compound 3 (140 mg, 0.5 mmol, 1.0 equiv) with Pd(OH)_{2} in anhydrous MeOH was stirred at rt. under an atmosphere of hydrogen for 1 day. The suspension was filtered through a pad of Celite® and washed several times with MeOH. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexanes/EtOAc, 9:1) to afford the expected product 19.
ESI(+)-HRMS: m/z calcd. for C_{16}H_{22}NO_{5} [M + H]^{+}: 308.1492; found: 308.1492.

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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588859. It contains 1H, APT (or 13C) and 2D (HSQC and/or COSY) NMR spectral data of all compounds in CDCl₃ and/or DMSO-ᴅ₆. It also contains HMBC of the compounds 1, 5 and 12c, NOESY NMR spectra of compounds 2, 3, 5, 6, 12c, 15a and 18, a figure comparing APT NMR of lyxofuranoside 1–3 and lyxopyranosides 5–7, a figure comparing 1H NMR among the compounds 1 and 5, and crude material of 5, and experimental procedures for the synthesis of starting materials 1–7 and compound 19.

**References**