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One-pot synthesis of vicinal aminoalkanols from sugar aldehydes

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ABSTRACT

A novel synthetic method of carbohydrate derived vicinal aminoalcohols, from sugar aldehydes and bromonitroalkanes, has been developed. It involves an indium-catalyzed one-pot Henry reaction and nitro group reduction, and proceeds with a remarkably high anti-selectivity. The reaction of the intermediate aminoalcohols with alkylating agents furnished the corresponding carbohydrate-based tertiary aminoalcohols with excellent stereoselectivity. This very simple methodology allows easy access to families of *N*,*N*-dialkylated vicinal aminoalkanols, useful intermediates in the synthesis of derivatives of biological interest and sugar-based stereodifferentiating agents for asymmetric catalysis.

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1. Introduction

In the past several years there has been increased pressure on the synthetic community to use environmentally benign or 'green' methods in synthesis. In this regard, the interest in the development of one-pot reactions for the sustainable synthesis of organic compounds has grown exponentially.[1] The use of one-pot conversions, reactions taking place without intermediate recovery steps, drastically reduces operating time and costs as well as consumption of solvents and energy.[2] In this context, reductive one-pot reactions involving carbonyl compounds and nitronates as carbon nucleophiles would be particularly attractive in assembling carbon–carbon bonds around the carbonyl group and directly generating a 1,2-aminoalkanol function.

The 1,2-aminoalkanol moiety is a structural component, which can be found in many naturally occurring molecules. For example, the vicinal aminoalkanol functionality is found in polyoxamic acid, a structural constituent of the nucleoside antibiotic polyoxin,[3] in indolizine alkaloids, such as 1,2-dihydroxyindolizine,[4] and in the potent antifungal sphingosine.[5] On other hand, chiral 1,2-aminoalkanols serve as useful intermediates in the synthesis of several natural products, as well as chiral auxiliaries and ligands for asymmetric synthesis.[6]

Sugar-derived 1,2-aminoalkanols are a particularly relevant family of compounds, not only for their usefulness as intermediates in the preparation of carbohydrate derivatives of biological interest, but also for their potential as stereodifferentiating agents in asymmetric catalysis.[7] Taking into account their importance in synthesis and biology, a short and reliable procedure for the multigram preparation of carbohydrate-based vicinal aminoalkanols would be of great interest. Although sugar-derived 1,2-aminoalcohol building blocks are present in the literature,[8] more efficient and practical routes that allow large-scale preparations reducing the environmental impact are still needed.[9]

In connection with our interest in the application of Barbier-type reactions to carbohydrate chemistry,[10] we have recently described[11] the efficient preparation of nitrosugars by means of the indium promoted addition of bromonitroalkanes to sugar aldehydes.[12] We have also described an indium-catalyzed version of the reaction, in which an excess of zinc was used as secondary reducing agent.[13] It is known that, in the presence of a proton source, zinc alone or in the presence of a catalytic amount of indium can reduce the nitro group to an amino group.[14] Then, we reasoned that adding a proton source to the reaction mixture, we could complete the one-pot Henry reaction-nitro reduction and obtain homologated aminosugars from sugar aldehydes. Herein we report the one-pot synthesis of several aminosugars, potentially useful as synthetic intermediates and ligands for metal catalysis.

2. Results and discussion

In order to set up the optimal conditions to carry out the synthesis of aminosugars, we started our study with the reaction of sugar aldehyde **1a** and bromonitromethane **2a** (Scheme 1). A

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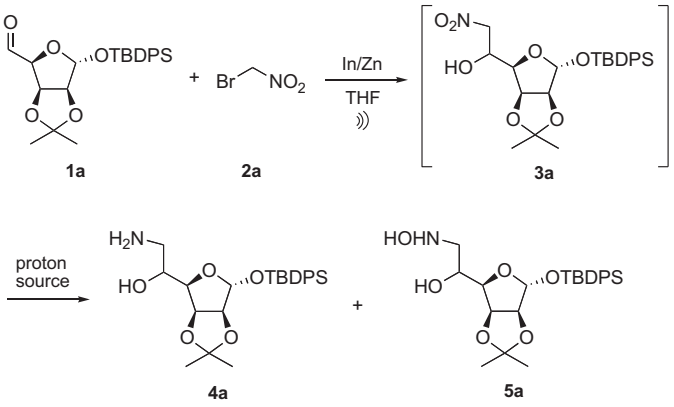


Scheme 1. One-pot synthesis of vicinal aminoalkanol **4a** from aldehyde **1a**.

mixture of aldehyde **1a** (1 equiv), bromonitromethane **2a** (1.2 equiv), indium (0.13 equiv), and zinc (10 equiv) was sonicated for 4 h. Then, after the formation of the corresponding nitrosugar, different conditions for the in situ nitro group reduction were investigated (Table 1).

Table 1
Conditions for the in situ reduction of the nitro group

Entry	Proton source	Conditions	**4a**:**5a**[a]	Yield[b] (**4a**)
1	NH_4Cl satd	rt/3 h	0:1	—
2	NH_4Cl satd	Reflux/3 h	1:1	n.d.
3	HCl 1 M/IPA	Reflux/3 h	1:0	31%
4	HCl 1 M/IPA	rt/3 h	2:1	n.d.
5	HCl 1 M/IPA	rt/12 h	1:0	52%
6	HCl 1 M/IPA	rt/12 h[c]	1:0	64%

IPA=isopropyl alcohol.
[a] Determined by ^1H NMR.
[b] After filtration over silica gel.
[c] Zinc (5 equiv) were added along with the proton source.

Addition of saturated aqueous ammonium chloride as proton source and reaction at room temperature afforded hydroxylamine **5a** as the only product, which is the intermediate product in the reduction of a nitro group to an amino group (entry 1). Rising the temperature to reflux, some of the desired nitroalkanol **4a** was obtained along with hydroxylamine **5a**. The use of 1 M aqueous hydrochloric acid as proton source has proven to be more convenient (entries 3–6). The best procedure in terms of conversion and cleanliness of the crude reaction consider the addition of isopropyl alcohol and diluted hydrochloric acid and the reaction at room temperature for 12 h (entries 5 and 6). Shorter reaction times yielded significant amounts of hydroxylamine **5a** (entry 4). On other hand, heating to reflux afforded a rather sluggish reaction crude, from which nitroalkanol was isolated in low yields (entry 3). The complete reduction of the nitro group to an amino group requires a catalytic amount of indium in the presence of an excess (10 molar equiv) of metal. Considering that some zinc is consumed in the formation of the nitronate, an extra amount of zinc could be required for the reduction step. Accordingly, the yields are slightly better when further 5 equiv of zinc were added together with the proton source (entry 6).

Using this methodology, a 90:10 diastereomeric mixture of aminoalcohols **4a** was obtained, being the anti-isomer the major compound obtained. Under these conditions, the formation of the intermediate hydroxylamine **5a** was not observed. The anti-selectivity comes from a C–O antibonding orbital energy lowering bringing an increased stabilization of a Felkin–Anh anti-periplanar nucleophilic addition of the organoindium species to the aldehyde carbonyl group (Fig. 1).[15] The addition of aqueous acid

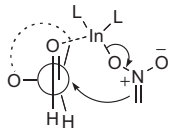
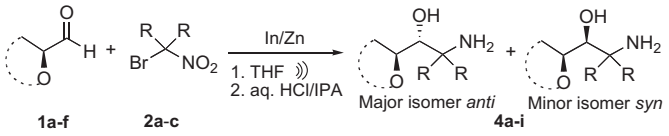


Fig. 1. Felkin–Ahn model for the attack of the indium nitronate on sugar aldehydes **1a**–**f**.

would cause, in the first instance, the formation of the nitroalcohol from the alkoxide. Then, the indium(0) in the presence of the proton source would reduce the nitro group to the corresponding amine. In the presence of zinc(0), the required indium(0) would be regenerated to continue the reduction until total conversion of the nitroalcohol into the corresponding aminoalcohol.

With the optimal conditions established, we studied the preparation of different aminosugars (Scheme 2) by reaction of sugar aldehydes **1a**–**g** with bromonitroalkanes **2a**–**c** (Fig. 2). The reaction is of general application regarding both the sugar aldehydes and the bromonitroalkanes, affording in all the cases the corresponding aminoalkanols as diastereomeric mixtures in which the anti-isomer is the major product, as predicted by the Felkin–Ahn model (Table 2).



Scheme 2. One-pot synthesis of aminoalkanols **4a**–**i** from sugar aldehydes **1a**–**f**.

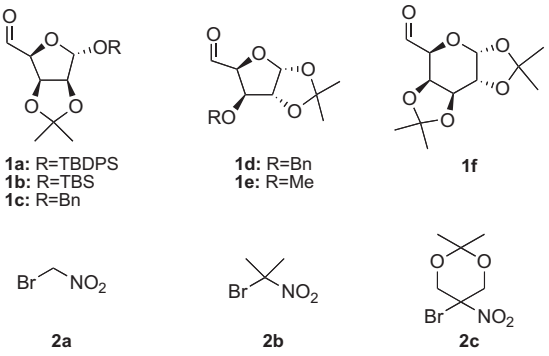


Fig. 2. Sugar aldehydes **1a**–**f** and bromonitroalkanes **2a**–**c**.

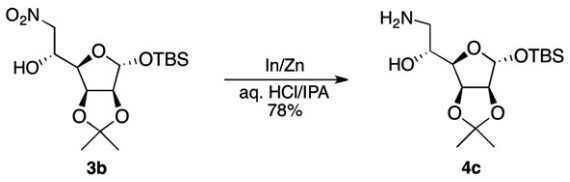
Table 2
Preparation of vicinal sugar-derived aminoalkanols **4a**–**i**

Entry	Sugar aldehyde	Bromonitro-alkane	Amino-alkanol	*anti*/*syn*[a]	Yield[b]
1	**1a**	**2b**	**4b**	100:0	52%
2	**1b**	**2c**	**4c**	100:0	54%
3	**1c**	**2a**	**4d**	78:22	61%
4	**1d**	**2b**	**4e**	85:15	49%
5	**1d**	**2c**	**4f**	76:24	51%
6	**1e**	**2a**	**4g**	69:31	62%
7	**1f**	**2a**	**4h**	87:13	64%
8	**1f**	**2c**	**4i**	100:0	52%

[a] Determined by ^1H NMR.
[b] After filtration over silica gel.

The preferential formation of the anti-isomers, as predicted by the Felkin–Ahn model, was confirmed when pure nitroalkanol **3b**[11a] was reduced by treatment with catalytic amount of indium

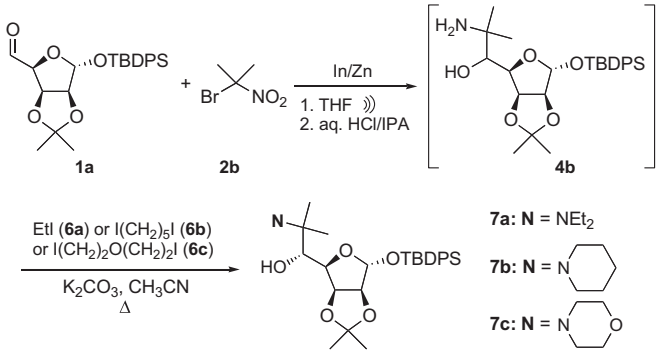
and an excess zinc in a mixture of 1 M HCl/IPA (Scheme 3). Under these conditions, pure anti-isomer of aminoalkanol **4c** was obtained in good yield.



Scheme 3. Reduction of nitroalkanol **3b** to aminoalkanol **4c**.

It is worth mentioning that this process tolerates a broad scope of sugar derived aldehydes bearing different protection on the hydroxyl groups. Also, all reactions took place with good stereoselectivities in absence of epimerization of any chiral center. The novel one-pot Henry reaction/nitro group reduction herein described has many advantages when compared to the previously reported procedures for the synthesis of sugar 1,2-aminoalkanols, usually prepared from sugar 1,2-diols as starting materials.[8] Firstly, the reaction is accompanied by concomitant formation of a C–C bond and homologation of the sugar chain. On other hand, as opposed to the aminoalkanols prepared from terminal diols, the amino group can be attached to a quaternary carbon. Finally, the procedure is very simple from the experimental point of view and the corresponding aminoalkanols are prepared in just one step from the starting sugar aldehydes, thus reducing waste and minimizing handling.

Carbohydrate derived tertiary aminoalkanols constitute an interesting family of ligands, which were used to promote a number of asymmetric transformations.[16] In order to obtain suitable intermediates for the synthesis of novel sugar-based ligands, we decided to investigate the application of the former strategy to the preparation of *N*,*N*-dialkyl vicinal aminoalkanols. Thus, after reaction of sugar aldehyde **1a** with 2-bromo-2-nitropropane **2b**, in the presence of zinc/indium, in situ nitro group reduction, by addition of diluted hydrochloric acid, and aqueous work-up, the crude mixture of the obtained aminoalkanols was dissolved in acetonitrile and heated in the presence of ethyl iodide **6a** and potassium carbonate (Scheme 4). The corresponding tertiary *anti*-amino-

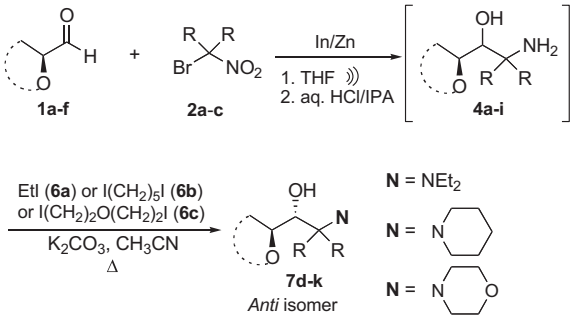


Scheme 4. Preparation of aminokanols **7a**–**c** from sugar aldehyde **1a** and 2-bromo-2-nitropropane **2b**.

alkanol **7a** was easily isolated from the reaction mixture in 39% yield. Similarly, reaction of the crude aminoalkanol with 1,2-diiodopentane **6b** or 2-iodoethyl ether **6c** afforded enantiomerically pure tertiary amines **7b** and **7c** in 43% and 45% yield, respectively.

Thus, this procedure allowed the straightforward preparation of carbohydrate-derived *N*,*N*-dialkyl-1,2-aminoalkanols **7a**–**c** from sugar aldehyde **1a** in two steps with just one final purification step.

Given the obtained satisfactory results, the synthesis of a family of tertiary aminoalcohol ligands was performed from aldehydes **1a**–**f** and bromonitroalkanes **2a**–**c**, via aminoalcohols **4a**–**i** (Scheme 5). Following the same strategy as above, the corresponding tertiary *anti*-aminoalkanols **7d**–**k** were isolated as pure compounds (Table 3). Thus, this procedure constitutes a general procedure for the straightforward preparation of carbohydrate-derived enantiomerically pure *N*,*N*-dialkyl-1,2-aminoalkanols **7a**–**k** from sugar aldehydes **1a**–**f** in two steps with just one final purification step.



Scheme 5. Synthesis of aminoalkanols **7d**–**k** from sugar aldehydes **1a**–**f** and bromonitroalkanes **2a**–**c**.

Table 3
Preparation of vicinal sugar-derived aminoalkanols

Entry	Aldehyde	Bromonitro alkane	Iodoalkane	Aminoalkanol	Yield
1	**1a**	**2a**	**6a**	**7d**	40%
2	**1b**	**2c**	**6a**	**7e**	39%
3	**1b**	**2c**	**6b**	**7f**	42%
4	**1c**	**2a**	**6a**	**7g**	38%
5	**1d**	**2b**	**6c**	**7h**	42%
6	**1d**	**2c**	**6b**	**7i**	47%
7	**1f**	**2a**	**6a**	**7j**	40%
8	**1f**	**2a**	**6b**	**7k**	49%

3. Conclusions

To sum up, we have developed a novel one-pot procedure consisting on an indium catalyzed Henry reaction/nitro group reduction that allows the preparation of carbohydrate derived vicinal aminoalkanols from sugar aldehydes. This process took place in good to excellent stereoselectivities maintaining the stereochemical integrity of the sugar backbone. The resulting 1,2-aminoalkanols can be directly employed in the synthesis of carbohydrate-based *N*,*N*-dialkyl-1,2-aminoalkanols, useful for the preparation of carbohydrate derivatives of biological interest as well as sugar-based tertiary aminoalcohol ligands. This methodology is very simple from the experimental point of view and would allow easy access to large families of *N*,*N*-dialkyl-1,2-aminoalkanols reducing the time and costs as well as consumption of solvents and energy.

It is also noteworthy that this is the first report of a sugar-based exocyclic *N*,*N*-dialkyl-1,2-aminoalkanol in which the amino function is attached to a quaternary carbon. These structures are more rigid, which is important for the development of effective ligands for asymmetric catalysis.

4. Experimental section

4.1. General experimental

Thin layer chromatography (TLC) was performed on aluminum sheets coated with 60 F_{254} silica gel, visualized using a spray of 0.2%

w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 0.5% ninhydrin in methanol. Purification via flash column chromatography was performed on Sorbsil C60 40/60 silica. Nuclear magnetic resonance spectroscopy (NMR) spectra were recorded on a Bruker Avance 300 spectrometer in the deuterated solvent stated. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 10 cm. Concentrations are quoted in g 100 mL^{-1}. Low resolution mass spectra were recorded using electrospray ionization (ESI), on Micromass BioQ II-ZS, Micromass 500 OAT, Micromass TofSpec 2E, Micromass GCT, or Micromass Platform 1 mass spectrometers. High resolution mass spectra (HRMS) were measured on a Waters 2790-Micromass LCT by ESI.

4.2. General procedure for the synthesis of aminoalcohols 4a–i

Bromonitroalkane (1.2 mmol) was added to a suspension of activated zinc powder (654 mg, 10.0 mol) and indium powder (14.3 mg, 0.13 mmol) in THF (5 mL) and the mixture was sonicated for 20 min. The corresponding aldehyde (1.0 mmol) was added and sonication was continued for a further 4 h. Then, isopropyl alcohol (11 mL), hydrochloric acid (8 mL, 1 M) and zinc (327 mg, 5.0 mmol) were added and the reaction mixture was stirred at room temperature for 14 h. The mixture was then neutralized with saturated aqueous sodium hydrogen carbonate, filtered through a pad of Celite and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. The residue was filtered through a pad of silica gel eluting with CH_2Cl_2 to CH_2Cl_2/MeOH 9:1.

*4.2.1. 6-Amino-1-O-tert-butyldiphenylsilyl-6-deoxy-2,3-di-O-isopropylidene-α-D-mannofuranose (**4a**).* $[\alpha]_D^{22}$ +0.6 (*c* 3.9, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.65–7.61 (m, 4H, Ar–H), 7.45–7.39 (m, 6H, Ar–H), 5.35 (s, 1H, 1H), 4.94 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.7 Hz, 1H, 3H), 4.70 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.04 (dd, $J_{4,5}$=8.5 Hz, $J_{4,3}$=3.7 Hz, 1H, 4H), 3.96–3.89 (m, 1H, 5H), 2.98 (dd, $J_{6,5}$=3.3 and $J_{6,6'}$=13.0 Hz, 1H, 6H), 2.75 (dd, $J_{6',5}$=7.8 and $J_{6',6}$=13.0 Hz, 1H, 6′H), 2.07 (br s, 3H, $-NH_2$, –OH), 1.40, 1.31 (2s, 6H, 2× CH_3), 1.06 [s, 9H, C(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.6, 135.5 (4× –CH–), 132.9, 132.6 (2× –C–), 130.0, 129.9, 127.8, 127.7 (6× –CH–), 112.6 (–C–), 101.6 (–CH–), 86.6, 80.8, 79.9, 77.2 (4× –CH–), 51.4 ($-CH_2-$), 26.7 [–C(CH_3)$_3$], 25.9, 24.7 (2× CH_3), 19.2 [–C(CH_3)$_3$]. MS (ESI^+) *m*/*z* (%) 458 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{25}H_{36}NO_5Si]^+$, $[M+H]^+$ 458.2357, found 458.2349.

*4.2.2. 5-[2-(Amino)propan-2-yl]-1-O-tert-butyldiphenylsilyl-2,3-di-O-isopropylidene-α-D-lyxofuranose (**4b**).* $[\alpha]_D^{22}$ +4.0 (*c* 1.0, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.68–7.60 (m, 4H, Ar–H), 7.41–7.35 (m, 6H, Ar–H), 5.35 (s, 1H, 1H), 4.98 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.4 Hz, 1H, 3H), 4.65 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.58 (br s, 3H, $-NH_2$, –OH), 4.19 (dd, $J_{4,5}$=8.9 and $J_{4,3}$=3.4 Hz, 1H, 4H), 3.75 (d, $J_{5,4}$=8.9 Hz, 1H, 5H), 1.42, 1.37 (2s, 6H, 2× CH_3), 1.09–0.94 (m, 15H, 2× CH_3, C(CH_3)$_3$), 0.94, 0.91 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.5, 135.4 (4× –CH–), 133.1, 132.8 (2× –C–), 129.9, 129.8, 127.7, 127.6 (6× –CH–), 112.1 (–C–), 101.8 (–CH–), 85.8, 81.1, 80.0, 69.9 (4× –CH–), 53.4 (–C–), 26.9 [–C(CH_3)$_3$], 25.9, 24.6, 19.4, 19.0 (4× CH_3), 18.2 (–C–). MS (ESI^+) *m*/*z* (%) 486 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{27}H_{40}NO_5Si]^+$ $[M+H]^+$ 486.2676 found 486.2682.

*4.2.3. 5-(5-Aminoethyl-2,2-dimethyl-1,3-dioxan-5-yl)-1-O-tert-butyldimethylsilyl-2,3-di-O-isopropylidene-α-D-lyxofuranose (**4c**).* $[\alpha]_D^{22}$ +2.6 (*c* 0.32, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=5.31 (s, 1H, 1H), 4.89 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.7 Hz, 1H, 3H), 4.49 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.17 (dd, $J_{4,5}$=8.77 and $J_{4,3}$=3.7 Hz, 1H, 4H), 4.05–3.97 (m, 2H, 2× –OCH–), 3.69–3.60 (m, 3H, 2× –OCH–, 5H), 1.97 (br s, 3H, $-NH_2$, –OH), 1.48, 1.44, 1.33 (3s, 12H, 4× CH_3), 0.88 [s, 9H, C(CH_3)$_3$], 0.11, 0.10 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=112.3, 101.7 (2× –C–), 98.2, 85.9, 81.2, 78.2, 71.0 (5× –CH–), 67.9, 66.9 (2× $-CH_2-$), 52.2 (–C–), 28.3, 26.0 (2× CH_3), 25.5 [–C(CH_3)$_3$], 24.6, 19.0 (2× CH_3), 17.9 [–C(CH_3)$_3$], –4.8, –5.4 (2× CH_3). MS (ESI^+) *m*/*z* (%) 434 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{20}H_{40}NO_7Si]^+$, $[M+H]^+$ 434.2561, found 434.2569.

*4.2.4. 6-Amino-1-O-benzyl-6-deoxy-2,3-di-O-isopropylidene-α-D-mannofuranose (**4d**).* $[\alpha]_D^{22}$ –8.0 (*c* 0.8, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.63–7.26 (m, 5H, Ar–H), 5.08 (s, 1H, 1H), 4.87 (dd, $J_{3,2}$=5.9 Hz, $J_{3,4}$=3.5 Hz, 1H, 3H), 4.70–4.47 (m, 3H, $-CH_2Ph$, 2H), 4.23–4.20 (m, 1H, 5H), 4.02 (dd, $J_{4,5}$=7.2 and $J_{4,3}$=3.5 Hz, 1H, 4H), 3.77–3.59 (m, 2H, 6H, 6′H), 2.12 (br s, 3H, $-NH_2$, –OH), 1.45, 1.30 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.5 (–C–), 128.4, 128.0, 127.9, 127.8 (5× –CH–), 112.5 (–C–), 105.6 (–CH–), 84.7, 81.4, 79.9 (3× –CH–), 69.2 ($-CH_2-$), 64.6 (–CH–), 54.7 ($-CH_2-$), 26.3, 24.5 (2× CH_3). MS (ESI^+) *m*/*z* (%) 310 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{16}H_{24}NO_5]^+$, $[M+H]^+$ 310.1654, found 310.1672.

*4.2.5. 5-[2-(Amino)propan-2-yl]-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (**4e**).* $[\alpha]_D^{22}$ –3.8 (*c* 0.3, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.38–7.28 (m, 5H, Ar–H), 5.99 (d, $J_{1,2}$=3.9 Hz, 1H, 1H), 4.72 (d, *J*=11.8 Hz, 1H, –CHPh), 4.59 (d, $J_{2,1}$=3.9 Hz, 1H, 2H), 4.54 (d, *J*=11.8 Hz, 1H, –CHPh), 4.27 (d, $J_{4,5}$=3.8 Hz, 1H, 4H), 4.10 (d, $J_{5,4}$=3.8 Hz, 1H, 5H), 4.02 (s, 1H, 3H), 1.51, 1.45, 1.31 (3s, 12H, 4× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=136.1 (–C–), 128.7, 128.3, 128.0 (5× –CH–), 112.2 (–C–), 104.9 (–CH–), 84.4, 81.6, 76.3, 72.6 (4× –CH–), 72.1 ($-CH_2-$), 57.9 (–C–), 26.9, 26.3, 23.6, 21.6 (4× CH_3). MS (ESI^+) *m*/*z* (%) 338 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{18}H_{28}NO_5]^+$, $[M+H]^+$ 338.1957, found 338.1962.

*4.2.6. 5-(5-Amino-2,2-dimethyl-1,3-dioxan-5-yl)-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose and 5-(5-amino-2,2-dimethyl-1,3-dioxan-5-yl)-3-O-benzyl-1,2-O-isopropylidene-α-L-arabinofuranose (**4f**).* ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.33 (m, 10H, Ar–H), 5.99 (d, $J_{1,2}$=3.9 Hz, 1H, 1H), 5.90 (d, $J_{1,2}$=3.8 Hz, 1H, 1H), 4.76–4.51 (m, 3H), 4.16–3.90 (m, 4H), 3.72–3.46 (m, 4H), 2.41 (br s, 3H, $-NH_2$, –OH), 1.46, 1.43, 1.42, 1.40, 1.32, 1.30 (6s, 24H, 8× CH_3). Major isomer anti (D-xylo): ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.3 (–C–), 128.7, 128.0, 127.8 (5× –CH–), 111.6 (–C–), 105.2 (–CH–), 98.1 (–C–), 82.7, 81.4, 78.8 (3× –CH–), 72.4 ($-CH_2-$), 69.4 (–CH–), 67.6, 66.6 (2× $-CH_2-$), 52.2 (–C–), 28.1, 26.8, 26.2, 18.9 (4× CH_3). Minor isomer *syn* (L-arabino): ^{13}C NMR (75 MHz, $CDCl_3$): δ=136.4 (–C–), 127.5, 128.3, 127.8 (5× –CH–), 111.6 (–C–), 105.2 (–CH–), 98.1 (–C–), 85.0, 81.7, 76.7 (3× –CH–), 72.0 ($-CH_2-$), 70.7 (–CH–), 67.1, 66.4 (2× $-CH_2-$), 51.9 (–C–), 26.9, 26.3, 25.4, 21.7 (4× CH_3). MS (ESI^+) *m*/*z* (%) 410 ($[M+H]^+$100); HRMS (ESI^+) calcd for $[C_{21}H_{32}NO_7]^+$ $[M+H]^+$ 410.2173, found 410.2198.

*4.2.7. 6-Amino-6-deoxy-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose (**4g**).* $[\alpha]_D^{22}$ +2.8 (*c* 0.6, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=5.91 (d, $J_{1,2}$=3.7 Hz, 1H, 1H), 4.55 (d, $J_{1,2}$=3.7 Hz, 1H, 2H), 4.32–4.28 (m, 1H), 4.14–4.10 (m, 1H), 3.89 (d, *J*=3.0 Hz, 1H), 3.46 (s, 3H, OCH_3), 3.44–3.38 (m, 1H, 6′H), 3.22–3.15 (m, 1H, 6H), 2.81 (br s, 1H, –OH), 1.48, 1.22 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=111.8 (–C–), 105.1 (–CH–), 83.4, 81.5, 81.264.8 (4× –CH–), 58.1 ($-CH_3$), 43.4 ($-CH_2-$), 26.7, 26.2 (2× CH_3). MS (ESI^+) *m*/*z* (%) 234 ($[M+H]^+$, 100); HRMS (ESI^+) calcd for $[C_{10}H_{20}NO_5]^+$, $[M+H]^+$ 234.1336, found 234.1314.

*4.2.8. 7-Deoxy-7-amino-1,2:3,4-di-O-isopropylidene-D-glycero-β-D-galactoheptose (**4h**).* $[\alpha]_D^{22}$ –6.2 (*c* 0.2, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=5.52 (d, $J_{1,2}$=5.1 Hz, 1H, 1H), 4.63 (dd, $J_{3,2}$=2.4 and $J_{3,4}$=8.0 Hz, 1H, 3H), 4.47 (dd, $J_{4,5}$=1.8 and $J_{4,3}$=8.0 Hz, 1H, 4H), 4.32 (dd, $J_{2,1}$=5.1 and $J_{2,3}$=2.4 Hz, 1H, 2H), 3.79–3.75 (m, 1H, 6H), 3.62 (dd, $J_{5,4}$=1.8 and $J_{5,6}$=8.7 Hz, 1H, 5H), 2.99 (dd, $J_{7,6}$=3.3 Hz,

$J_{7,7'}$=13.0 Hz, 1H, 7H), 2.85 (dd, $J_{7',6}$=6.1 and $J_{7',7}$=13.0 Hz, 1H, 7′H), 1.96 (br s, 3H, −NH_2, −OH), 1.52, 1.46, 1.37, 1.33 (4s, 12H, 4× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=109.2, 108.5 (2× −C−), 96.4 (−CH−), 70.8, 70.6, 70.5, 69.4, 68.0 (5× −CH−), 43.8 (−CH_2−), 26.0, 25.9, 24.9, 24.4 (4× CH_3). MS (ESI^+) *m*/*z* (%) 290 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{13}H_{24}NO_6]^+$, [M+H]$^+$ 290.1595, found 290.1598.

*4.2.9. 6-(5-Amino-2,2-dimethyl-1,3-dioxan-5-yl)-1,2:3,4-di-O-isopropylidene-β-D-galactopyranose (**4i**).* $[\alpha]_D^{22}$ −2.1 (*c* 2.5, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.49 (d, $J_{1,2}$=5.1 Hz, 1H, 1H), 4.61 (dd, $J_{3,2}$=2.4 and $J_{3,4}$=8.0 Hz, 1H, 3H), 4.45 (dd, $J_{4,5}$=1.7 and $J_{4,3}$=8.0 Hz, 1H, 4H), 4.30 (dd, $J_{2,1}$=5.1 and $J_{2,3}$=2.4 Hz, 1H, 2H), 4.08 (d, *J*=12.0 Hz, 1H, −CHO−), 4.04 (d, *J*=12.0 Hz, 1H, −CHO−), 3.82 (dd, $J_{5,4}$=1.7 and $J_{5,6}$=9.1 Hz, 1H, 5H), 3.66−3.50 (m, 3H, 6H, 2× −CHO−), 2.58 (br s, 3H, −NH_2, −OH), 1.55, 1.45, 1.44, 1.41, 1.36, 1.31 (6s, 18H, 6× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=109.0, 108.5, 98.0 (3× −C−), 96.3 (−CH−), 71.2, 70.5, 70.3, 69.9 (4× −CH−), 67.4, 66.7 (2× −CH_2−), 66.5 (−CH−), 52.4 (−C−), 28.7, 25.9, 25.8, 24.7, 24.3, 18.5 (6× CH_3). MS (ESI^+) *m*/*z* (%) 390 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{18}H_{32}NO_8]^+$, [M+H]$^+$ 390.2116, found 390.2122.

4.3. General procedure for the synthesis of ligands 7a, 7d, 7e, 7g, and 7j

Bromonitroalkane (1.2 mmol) was added to a suspension of activated zinc powder (654 mg, 10.0 mol) and indium powder (14.3 mg, 0.12 mmol) in THF (5 mL) and the mixture was sonicated for 20 min. The corresponding aldehyde (1.0 mmol) was added and sonication was continued for a further 4 h. Then, isopropyl alcohol (11 mL), hydrochloric acid (8 mL, 1 M) and zinc (325 mg, 5.0 mmol) were added and the reaction mixture was stirred at room temperature for 14 h. The mixture was then neutralized with saturated aqueous sodium hydrogen carbonate, filtered through a pad of Celite and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Ethyl iodide (112 μL, 1.35 mmol) and potassium carbonate (9.5 mmol) were added to a solution of the obtained crude aminoalcohol (0.5 mmol) in acetonitrile (4 mL) and the resulting mixture was heated at 60 °C for a total of 60 h. Further portions of ethyl iodide were added after 10 h (56 μL, 0.7 mmol), 22 h (37 μL, 0.45 mmol), 30 h (37 μL, 0.45 mmol) and 54 h (20 μL, 0.25 mmol). The reaction mixture was cooled, filtered, and evaporated under reduced pressure and the residue was purified by flash column chromatography in mixtures of dichloromethane/methanol.

*4.3.1. 1-O-tert-Butyldiphenylsilyl-2,3-di-O-isopropylidene-5-[2-(N,N-diethylamino)propan-2-yl]-α-D-lyxofuranose (**7a**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ +14.9 (*c* 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68−7.61 (m, 4H, Ar−H), 7.42−7.35 (m, 6H, Ar−H), 5.36 (s, 1H, 1H), 5.00 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.5 Hz, 1H, 3H), 4.69 (d, $J_{2,3}$=5.8 Hz, 2H, 2H), 4.14 (dd, $J_{4,5}$=9.0 and $J_{4,3}$=3.5 Hz, 1H, 4H), 3.79 (d, $J_{5,4}$=9.0 Hz, 1H, 5H), 2.80−2.78 [m, 4H, −(CH_2CH_3)$_2$], 1.41, 1.35 (2s, 6H, 2× CH_3), 1.19−1.07 [m, 21H, 2× CH_3, (CH_2CH_3)$_2$, C(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.5, 135.4 (4× −CH−), 133.0, 132.8 (2× −C−), 129.9, 129.8, 127.7, 127.6 (6× −CH−), 112.3 (−C−), 102.1 (−CH−), 86.0, 81.1, 80.0, 69.9 (4× −CH−), 53.4 (−C−), 42.1 (2× −CH_2−), 26.6 [−C(CH_3)$_3$], 25.9, 24.7, 19.5, 19.4, 19.1 (6× CH_3), 18.0 (−C−). MS (ESI^+) *m*/*z* (%) 542 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{31}H_{48}NO_5Si]^+$, [M+H]$^+$ 542.3287, found 542.3296. R_f=0.27 (dichloromethane/methanol 39:1).

*4.3.2. 1-O-tert-Butyldiphenylsilyl-6-deoxy-6-N,N-diethylamino-2,3-di-O-isopropylidene-α-D-mannofuranose (**7d**).* Flash column chromatography eluting with dichloromethane/methanol 19:1. $[\alpha]_D^{23}$ +15.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67−7.61 (m, 4H, Ar−H), 7.46−7.38 (m, 6H, Ar−H), 5.35 (s, 1H, 1H), 5.00 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.3 Hz, 1H, 3H), 4.73 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.59−4.29 (m, 2H, 4H, 5H), 3.53−3.34 (m, 6H, 6H, 6′H, 2× −CH_2−), 2.73 (d, *J*=14.3 Hz, 1H, O*H*), 1.42, 1.33 (2s, 6H, 2× CH_3), 1.30−1.26 (m, 6H, 2× CH_3), 1.07 [s, 9H, −C(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.7, 135.6 (4× −CH−), 135.6, 132.3 (2× −C−), 129.9, 129.7, 127.7, 127.6 (6× −CH−), 112.7 (−C−), 102.0 (−CH−), 86.7, 80.2, 79.2, 63.8 (4× −CH−), 59.6 (−CH_2−), 54.3 (2× −CH_2−), 26.7 [−C(CH_3)$_3$], 26.2, 24.6 (2× CH_3), 18.9 [−C(CH_3)$_3$], 7.7 (2× CH_3). MS (ESI^+) *m*/*z* (%) 514 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{29}H_{44}NO_5Si]^+$, [M+H]$^+$ 514.2989, found 514.3001. R_f=0.34 (dichloromethane/methanol 19:1).

*4.3.3. 1-O-tert-Butyldimethylsilyl-5-(5-N,N-diethylamino-2,2-dimethyl-1,3-dioxan-5-yl)-2,3-di-O-isopropylidene-α-D-lyxofuranose (**7e**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ +3.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.30 (s, 1H, 1H), 4.88 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.6 Hz, 1H, 3H), 4.48 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.10−4.02 (m, 2H, −OCH_2−), 3.98 (dd, $J_{4,5}$=9.3 and $J_{4,3}$=3.6 Hz, 1H, 4H), 3.69 (AB, *J*=12.1 Hz, 2H, −OCH_2−), 3.57 (d, $J_{5,4}$=9.3 Hz, 1H, 5H), 3.00 (br s, 1H, −OH), 2.77−2.60 (m, 4H, 2× −CH_2−), 1.46, 1.40, 1.34 (3s, 12H, 4× CH_3), 1.16−1.12 (m, 6H, 2× CH_3), 0.88 [s, 9H, −C(CH_3)$_3$], 0.13, 0.11 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=112.3, 101.7 (2× −C−), 98.3, 85.9, 81.0, 78.7, 67.0 (5× −CH−), 63.5, 63.0 (2× −CH_2−), 55.3 (−C−), 36.3 (2× −CH_2−), 28.9, 26.0 (2× CH_3), 25.5 [−C(CH_3)$_3$], 24.6, 18.9 (2× CH_3), 17.9 [−C(CH_3)$_3$], 15.91 (2× CH_3), −4.8, −5.4 (2× CH_3). MS (ESI^+) *m*/*z* (%) 490 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{24}H_{48}NO_7Si]^+$, [M+H]$^+$ 490.3200, found 490.3219. R_f=0.33 (dichloromethane/methanol 39:1).

*4.3.4. 1-O-Benzyl-6-deoxy-6-N,N-diethylamino-2,3-di-O-isopropylidene-α-D-mannofuranose (**7g**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ +37.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35−7.26 (m, 5H, Ar−H), 5.08 (s, 1H, 1H), 4.87 (dd, $J_{3,2}$=5.9 and $J_{3,4}$=3.5 Hz, 1H, 3H), 4.65−4.48 (m, 3H, −CH_2Ph, 2H), 4.13−3.96 (m, 1H, 5H), 3.74 (dd, $J_{4,5}$=8.3 and $J_{4,3}$=3.5 Hz, 1H, 4H), 2.98−2.93 (m, 1H, −OH), 2.65−2.24 (m, 4H, 6H, 6′H, −CH_2−), 2.04−1.99 (m, 2H, −CH_2−), 1.51−1.25 (m, 12H, 4× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.5 (−C−), 128.4, 128.0, 127.8 (5× −CH−), 112.6 (−C−), 106.0 (−CH−), 84.7, 81.5, 78.0 (3× −CH−), 69.3 (−CH_2−), 64.6 (−CH−), 61.3, 54.8, 49.9 (3× −CH_2−), 28.3, 26.4, 26.0, 24.6 (4× CH_3). MS (ESI^+) *m*/*z* (%) 366 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{18}H_{32}NO_6]^+$, [M+H]$^+$ 366.2275, found 366.2288. R_f=0.30 (dichloromethane/methanol 39:1).

*4.3.5. 7-Deoxy-7-N,N-diethylamino-1,2:3,4-di-O-isopropylidene-D-glycero-β-D-galacto-heptose (**7j**).* Flash column chromatography eluting with dichloromethane/methanol 19:1. $[\alpha]_D^{23}$ +11.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.51 (d, $J_{1,2}$=5.0 Hz, 1H, 1H), 4.65 (dd, $J_{3,2}$=2.4 and $J_{3,4}$=7.9 Hz, 1H, 3H), 4.47 (dd, $J_{4,5}$=1.8 and $J_{4,3}$=7.9 Hz, 1H, 4H), 4.41−4.36 (m, 1H, 6H), 4.34 (dd, $J_{2,1}$=5.0 and $J_{2,3}$=2.4 Hz, 1H, 2H), 3.83 (dd, $J_{5,4}$=1.8 and $J_{5,6}$=7.4 Hz, 1H, 5H), 3.50−3.26 (m, 6H, 7H, 7′H, 2× −CH_2−), 2.05−2.09 (m, 1H, −OH), 1.56−1.47 (m, 12H, 4× CH_3), 1.33, 1.37 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=109.5, 109.0 (2× −C−), 96.1 (−CH−), 70.4, 70.3, 69.9, 69.1, 64.7 (5× −CH−), 55.8, 50.0, 45.6 (3× −CH_2−), 54.3 (2× −CH_2−), 26.2, 25.9, 24.7, 24.2 (4× CH_3), 10.0, 9.8 (2× CH_3). MS (ESI^+) *m*/*z* (%) 346 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{17}H_{32}NO_6]^+$, [M+H]$^+$ 346.2224, found 346.2218. R_f=0.32 (dichloromethane/methanol 19:1).

4.4. General procedure for the synthesis of ligands 7b, 7f, 7i, and 7k

Bromonitroalkane (1.2 mmol) was added to a suspension of activated zinc powder (654 mg, 10.0 mol) and indium powder

(14.3 mg, 0.12 mmol) in THF (5 mL) and the mixture was sonicated for 20 min. The corresponding aldehyde (1.0 mmol) was added and sonication was continued for a further 4 h. Then, isopropyl alcohol (11 mL), hydrochloric acid (8 mL, 1 M) and zinc (325 mg, 5.0 mmol) were added and the reaction mixture was stirred at room temperature for 14 h. The mixture was then neutralized with saturated aqueous sodium hydrogen carbonate, filtered through a pad of Celite and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. 1,5-Diiodopentane (75 μL, 0.5 mmol) and potassium carbonate (70 mg, 0.5 mmol) were added to a solution of the obtained crude aminoalcohol (0.5 mmol) in acetonitrile (4 mL), and the resulting mixture was heated at 60 °C for a total of 12 h, and then at 80 °C for 12 h. Further 1,5-diiodopentane was added (38 μL, 0.25 mmol) and the mixture was heated at 80 °C for further 12 h, and then refluxed for 24 h. The reaction mixture was cooled, filtered, and evaporated under reduced pressure and the residue was purified by flash column chromatography in mixtures of dichloromethane/methanol.

*4.4.1. 1-O-tert-Butyldiphenylsilyl-2,3-di-O-isopropylidene-5-[2-(piperidin-1-yl)propan-2-yl]-α-D-lyxofuranose (**7b**).* Flash column chromatography eluting with dichloromethane/methanol 19:1. $[\alpha]_D^{23}$ +11.2 (*c* 3.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=7.69–7.62 (m, 4H, Ar–H), 7.40–7.34 (m, 6H, Ar–H), 5.35 (s, 1H, 1H), 5.00 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.5 Hz, 1H, 3H), 4.70 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.12 (dd, $J_{4,5}$=9.1 and $J_{4,3}$=3.5 Hz, 1H, 4H), 3.77 (d, $J_{5,4}$=9.1 Hz, 1H, 5H), 2.69–2.42 (m, 4H, 2× $-CH_2$), 1.62–1.44 (m, 4H, 2× $-CH_2-$), 1.49–1.36 (m, 5H, $-CH_2-$, CH_3), 1.41 (s, 3H, CH_3), 1.07 [s, 9H, $-C(CH_3)_3$], 0.94, 0.87 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.5, 135.4 (4× –CH–), 133.0, 132.2 (2× –C–), 129.8, 129.7, 127.7, 127.5 (6× –CH–), 112.2 (–C–), 102.0 (–CH–), 86.1, 81.3, 80.0, 69.5 (4× –CH–), 53.7 (–C–), 46.2 (2× $-CH_2-$), 26.6 [$-C(CH_3)_3$], 25.9 (2× $-CH_2-$), 25.1, 24.7 (2× CH_3), 24.4 ($-CH_2-$), 19.3 [$-C(CH_3)_3$], 19.1, 17.4 (2× CH_3). MS (ESI^+) *m*/*z* (%) 554 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{32}H_{48}NO_5Si]^+$, [M+H]$^+$ 554.3288, found 497.3296. R_f=0.34 (dichloromethane/methanol 19:1).

*4.4.2. 1-O-tert-Butyldimethylsilyl-2,3-di-O-isopropylidene-5-[2,2-dimethyl-5-(piperidin-1-yl)-1,3-dioxan-5-yl]-α-D-lyxofuranose (**7f**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ –3.2 (*c* 3.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=5.32 (s, 1H, 1H), 4.87 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.6 Hz, 1H, 3H), 4.48 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.20 (d, *J*=12.9 Hz, 1H, –OCH–), 4.08 (d, *J*=12.9 Hz, 1H, –OCH–), 3.97–3.89 (m, 3H, 2× –OCH–, 4H), 3.48 (d, $J_{5,4}$=9.3 Hz, 1H, 5H), 2.92–2.84 (m, 4H, 2× $-CH_2-$), 1.68–1.55 (m, 4H, 2× $-CH_2-$), 1.51–1.46 (m, 8H, $-CH_2$, 2× CH_3), 1.39, 1.34 (2s, 6H, 2× CH_3), 0.88 [s, 9H, $-C(CH_3)_3$], 0.12, 0.10 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=112.3 (–C–), 101.6 (–CH–), 98.1 (–C–), 85.9, 81.1, 79.1, 66.7 (4× –CH–), 62.2, 62.0 (2× $-CH_2-$), 58.3 (–C–), 49.5 (2× $-CH_2-$), 28.3 ($-CH_3$), 27.7 (2× $-CH_2-$), 26.0 (CH_3), 25.5 [$-C(CH_3)_3$], 24.7 (CH_3), 24.6 ($-CH_2-$), 19.7 [$-C(CH_3)_3$], 17.9 (CH_3), –4.7, –5.4 (2× CH_3). MS (ESI^+) *m*/*z* (%) 502 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{25}H_{48}NO_7Si]^+$, [M+H]$^+$ 502.3189, found 502.3194. R_f=0.28 (dichloromethane/methanol 39:1).

*4.4.3. 3-O-Benzyl-1,2-O-isopropylidene-5-[2,2-dimethyl-5-(piperidin-1-yl)-1,3-dioxan-5-yl]-α-D-xylofuranose (**7i**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{24}$ –38.0 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, Ar–H), 5.90 (d, $J_{1,2}$=3.7 Hz, 1H, 1H), 4.68 (s, 2H, $-CH_2Ph$), 4.51 (d, $J_{2,3}$=3.7 Hz, 1H, 2H), 4.20–3.87 (m, 6H, 2× $-OCH_2-$, 3H, 4H), 3.53 (d, $J_{5,4}$=9.3 Hz, 1H, 5H), 2.93–2.84 (m, 4H, 2× $-CH_2-$), 1.63–1.59 (m, 4H, 2× $-CH_2-$), 1.52–1.46 (m, 8H, $-CH_2-$, 2× CH_3), 1.38, 1.30 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.8 (–C–), 128.4, 127.8 (5× –CH–), 111.7 (–C–), 105.3 (–CH–), 98.2 (–C–), 83.0, 81.9, 79.7 (3× –CH–), 72.9 ($-CH_2-$), 65.8 (–CH–), 62.3, 62.3 (2× $-CH_2-$), 58.7 (–C–), 49.5 (2× $-CH_2-$), 28.3 (CH_3), 27.8 (2× $-CH_2-$), 26.8, 26.3 (2× CH_3), 24.6 ($-CH_2-$), 19.4 (CH_3). MS (ESI^+) *m*/*z* (%) 478 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{26}H_{40}N_2O_7]^+$, [M+H]$^+$ 478.2790, found 478.2790. R_f=0.27 (dichloromethane/methanol 39:1).

*4.4.4. 7-Deoxy-7-(piperidin-1-yl)-1,2:3,4-di-O-isopropylidene-glycero-β-D-galacto-heptose (**7k**).* Flash column chromatography eluting with dichloromethane/methanol 19:1. $[\alpha]_D^{23}$ –16.4 (*c* 3.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=5.48 (d, $J_{1,2}$=5.0 Hz, 1H, 1H), 4.64–4.58 (m, 2H, 3H, –OH), 4.49 (dd, $J_{4,5}$=1.7 Hz, $J_{4,3}$=8.0 Hz, 1H, 4H), 4.31 (dd, $J_{2,1}$=5.0 and $J_{2,3}$=2.2 Hz, 1H, 2H), 4.29–4.22 (m, 1H, 6H), 4.71 (dd, $J_{2,1}$=5.0 Hz, $J_{2,3}$=2.3 Hz, 1H, 2H), 3.16–2.95 (m, 6H, 7H, 7′H, 2× $-CH_2-$), 1.98–1.93 (m, 4H, 2× $-CH_2-$), 1.66–1.62 (m, 2H, $-CH_2-$), 1.55, 1.45, 1.36, 1.32 (4s, 12H, 4× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=109.1, 108.7 (2× –C–), 96.0 (–CH–), 70.5, 70.2, 69.8, 69.2, 63.7 (5× –CH–), 61.1, 54.5 (3× $-CH_2-$), 26.1, 25.8, 24.7, 24.0 (4× CH_3), 23.4, 22.3 (3× $-CH_2-$). MS (ESI^+) *m*/*z* (%) 358 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{18}H_{32}NO_6]^+$, [M+H]$^+$ 358.2217, found 358.2224. R_f=0.32 (dichloromethane/methanol 19:1).

4.5. General procedure for the synthesis of ligands 7c and 7h

Bromonitroalkane (1.2 mmol) was added to a suspension of activated zinc powder (654 mg, 10.0 mol) and indium powder (14.3 mg, 0.12 mmol) in THF (5 mL) and the mixture was sonicated for 20 min. The corresponding aldehyde (1.0 mmol) was added and sonication was continued for a further 4 h. Then, isopropyl alcohol (11 mL), hydrochloric acid (8 mL, 1 M) and zinc (325 mg, 5.0 mmol) were added and the reaction mixture was stirred at room temperature for 14 h. The mixture was then neutralized with saturated aqueous sodium hydrogen carbonate, filtered through a pad of Celite and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. 2-Iodoethyl ether (71 μL, 0.5 mmol) and potassium carbonate (70 mg, 0.5 mmol) were added to a solution of the obtained crude aminoalcohol (0.5 mmol) in acetonitrile (4 mL) and the resulting mixture was heated at 60 °C for a total of 12 h, and then at 80 °C for 12 h. Further 2-iodoethyl ether was added (36 μL, 0.25 mmol) and the mixture was heated at 80 °C for further 12 h, and then refluxed for 24 h. The reaction mixture was cooled, filtered, and evaporated under reduced pressure and the residue was purified by flash column chromatography in mixtures of dichloromethane/methanol.

*4.5.1. 1-O-tert-Butyldiphenylsilyl-2,3-di-O-isopropylidene-5-[2-(morpholino)propan-2-yl]-α-D-lyxofuranose (**7c**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ +11.0 (*c* 7.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=7.69–7.62 (m, 4H, Ar–H), 7.44–7.35 (m, 6H, Ar–H), 5.35 (s, 1H, 1H), 5.00 (dd, $J_{3,2}$=5.8 and $J_{3,4}$=3.5 Hz, 1H, 3H), 4.70 (d, $J_{2,3}$=5.8 Hz, 1H, 2H), 4.12 (dd, $J_{4,5}$=9.0 and $J_{4,3}$=3.5 Hz, 1H, 4H), 3.72–3.69 (m, 5H, 5H, 2× $-CH_2O-$), 2.61–2.49 (m, 4H, 2× $-CH_2-$), 1.60 (br s, 1H, –OH), 1.41, 1.36 (2s, 6H, 2× CH_3), 1.06 [s, 9H, $-C(CH_3)_3$], 0.94, 0.91 (2s, 6H, 2× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.5, 135.4 (4× –CH–), 133.1, 132.9 (2× –C–), 129.8, 129.7, 127.7, 127.6 (6× –CH–), 112.2 (–C–), 102.1 (–CH–), 86.1, 81.3, 79.7, 69.3 (4× –CH–), 67.7 (2× $-CH_2-$), 59.3 (–C–), 45.4 (2× $-CH_2-$), 26.6 [$-C(CH_3)_3$], 25.9, 24.7 (2× CH_3), 19.1 [$-C(CH_3)_3$], 18.9, 17.0 (2× CH_3). MS (ESI^+) *m*/*z* (%) 556 ([M+H]$^+$, 100); HRMS (ESI^+) calcd for $[C_{31}H_{46}NO_6Si]^+$, [M+H]$^+$ 556.3080, found 556.3089. R_f=0.27 (dichloromethane/methanol 39:1).

*4.5.2. 3-O-Benzyl-1,2-O-isopropylidene-5-[2-(morpholino)propan-2-yl]-α-D-xylofuranose (**7h**).* Flash column chromatography eluting with dichloromethane/methanol 39:1. $[\alpha]_D^{23}$ –20.9 (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, H–Ar), 5.90 (d,

$J_{1,2}$=3.7 Hz, 1H, H-1), 4.72–4.45 (m, 5H), 4.88–4.76 (m, 2H), 3.79–3.51 (m, 3H), 2.30–2.70 (m, 4H, 2× $-CH_2$), 1.46, 1.38, 1.10, 0.92 (4s, 12H, 4× CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.4 (−C−), 129.0, 128.5, 128.2 (5× −CH−), 112.3 (−C−), 105.2 (−CH−), 84.8, 82.2, 77.4 (3× −CH−), 72.0 ($-CH_2-$), 71.3 (−CH−), 68.3 (2× $-CH_2-$), 59.7 (−C−), 46.7 (2× $-CH_2-$), 27.4, 27.0, 19.6, 19.2 (4× CH_3). MS (ESI$^+$) m/z (%) 408 ($[M+H]^+$, 100); HRMS (ESI$^+$) calcd for $[C_{22}H_{34}NO_6]^+$, $[M+H]^+$ 408.2381, found 408.2397. R_f=0.27 (dichloromethane/methanol 39:1).

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Supplementary data

^{1}H and ^{13}C NMR spectra for vicinal aminoalkanols **7**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.072.

References and notes

1. (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329; (b) Neuschütz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227; (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (d) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137; (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195; (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (g) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
2. Bruggink, A.; Schoevaart, R.; Kieboom, T. *Org. Process Res. Dev.* **2003**, *7*, 622.
3. (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7499; (b) Paz, M.; Sardina, F. *J. Org. Chem.* **1993**, *58*, 6990; (c) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479; (d) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139; (e) Matsura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733; (f) Jackson, R. F.; Palmer, N. J.; Wyther, M. J.; Clegg, W.; Elsegood, M. *J. Org. Chem.* **1995**, *60*, 6431; (g) Kang, S. H.; Choi, H. *Chem. Commun.* **1996**, 1521; (h) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 119.
4. (a) Harris, T. M.; Harris, C. M. H.; Hill, J. E.; Ungemach, F. S.; Broquist, H. P.; Wickwire, B. M. *J. Org. Chem.* **1987**, *52*, 3094; (b) Heitz, M.-P.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 2591.
5. Payne, C. D.; Ray, T. L.; Downing, D. T. *J. Invest. Dermatol.* **1996**, *106*, 549.
6. (a) Ager, D. J.; Prakash, I.; Scheed, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
7. Le, T. T.; Guillarme, S.; Saluzzo, C. *Tetrahedron* **2010**, *66*, 8893.
8. (a) Sudershan, K. S.; Thompson, D. S.; Akhtar, M. N. US 5360792 A 19941101. (b) Sudershan, K. S.; Thompson, D. S.; Akhtar, M. N. WO 9313117 A2 19930708.
9. Mancilla, G.; Durán-Patrón, R. M.; Macías-Sánchez, A. J.; Collado, I. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6820 and references cited herein.
10. (a) Soengas, R. G. *Tetrahedron Lett.* **2010**, *51*, 105; (b) Soengas, R. G. *Tetrahedron: Asymmetry* **2011**, *217*, 2249; (c) Soengas, R. G.; Estévez, A. M. *Synlett* **2011**, 2625; (d) Soengas, R. G. *Synlett* **2011**, 2547; (e) Soengas, R. G.; Segade, Y.; Jiménez, C.; Rodríguez, J. *Tetrahedron* **2011**, *67*, 2617; (f) Soengas, R. G. *Ultrason. Sonochem.* **2012**, *19*, 916.
11. (a) Soengas, R. G.; Estévez, A. M. *Eur. J. Org. Chem.* **2010**, 5190; (b) Soengas, R. G.; Estévez, A. M. *Tetrahedron Lett.* **2012**, *53*, 570; (c) Rodríguez-Solla, H.; Soengas, R. G.; Alvaredo, N. *Synlett* **2012**, 2083.
12. Reaction of bromonitromethane and aldehydes to give 2-bromo-2-nitroalkan-1-ols has also been described. See Ref. 11c and: (a) Alcaide, B.; Almendros, P.; Luna, A.; Torres, R. *Org. Biomol. Chem.* **2008**, *6*, 1635; (b) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; García-Granda, S.; Díaz, M. R. *Org. Lett.* **2006**, *8*, 5979; (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Commun.* **2008**, 4840.
13. Soengas, R. G.; Silva, A. M. S. *Synlett* **2012**, 873.
14. Bernardi, L.; Bonini, B. F.; Capitó, E.; Dessole, G.; Comes-Franchini, M.; Fochi, M.; Ricci, A. *J. Org. Chem.* **2004**, *69*, 8168.
15. (a) Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199; (b) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dau, M.-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146; (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
16. (a) Emmerson, D. P. G.; Villard, R.; Mugnaini, C.; Batsanov, A.; Howard, J. A. K.; Hems, W. P.; Tooze, R. P.; Davis, B. G. *Org. Biomol. Chem.* **2003**, *1*, 3826; (b) Emmerson, D. P. G.; Hems; Davis, B. G. *Tetrahedron: Asymmetry* **2005**, *16*, 213; (c) Cho, B. T.; Kim, N. *Synth. Commun.* **1996**, *26*, 855.