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An improved methodology for the synthesis of 1-*C*-allyl imino-D-xylitol and -L-arabinitol and their rapid functionalization

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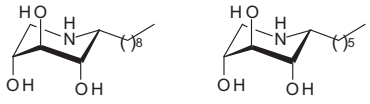
ABSTRACT

As part of our research program dedicated to the design and synthesis of new iminosugars as pharmacological chaperones for the treatment of lysosomal storage disorders, we developed a rapid and efficient methodology for the access to functionalized and non-functionalized 1-*C*-alkylated derivatives in the D-*xylo* and L-*arabino* series. These compounds, as *gluco* and *galacto* mimics, were designed to be potent inhibitors of, respectively, β-glucocerebrosidase, involved in Gaucher disease, and β-galactocerebrosidase, responsible for Krabbe disease. The key step of the synthesis is the diastereoselective addition of allyltrimethylsilane to the D-*xylo* or L-*arabino* *N*-benzyloxycarbonyl protected glycopyranosylamine. This protective group allows the direct functionalization of the obtained iminosugars using metathesis or oxidation reactions. For determination of the absolute configuration of dihydroxylation reaction products the in situ dimolybdenum methodology of electronic circular dichroism spectroscopy was successfully used.

1. Introduction

Lysosomal storage disorders (LSD) are inherited and rare diseases caused by an impaired catabolism of glycolipids in the lysosome.[1] Mutations in the glycosidases responsible for the hydrolysis of these macromolecules promote their elimination from cells by the protein quality control mechanisms, leading to the accumulation of their undegraded substrates. Gaucher disease, the most prevalent LSD, is due to the deficiency of β-glucocerebrosidase (GCase), the hydrolase responsible for the cleavage of glucosylceramide β-glycosidic bond.[2] Two strategies are currently approved for the treatment of Gaucher disease, namely Enzyme Replacement Therapy (ERT) and Substrate Reduction Therapy (SRT).[3] ERT consists of the injection of recombinant GCase, while SRT uses small molecules acting as inhibitors of the glucosylceramide biosynthesis. A third strategy, Pharmacological Chaperone Therapy (PCT) is currently under clinical trials for several LSD. Small molecules acting as pharmacological chaperones are believed to stabilize the conformation of the deficient, but still active enzyme and allow it to bypass the quality control barriers and to be transported to the lysosome; the activity of the deficient enzyme is thus increased and excess glucosylceramide can be hydrolyzed, leading to a significant decrease of disease symptoms.[4] Iminosugars, as potent glycosidase inhibitors, were found to be active at low concentrations as good chaperone molecules for lysosomal enzymes as they strongly interact with their active site.[5] Our group first focused its investigations on the design and synthesis of new iminosugars as potential pharmacological chaperones for GCase.[6] α-1-*C*-Nonyl imino-D-xylitol **1** (α-C_9-DIX, Fig. 1) was found to be a powerful inhibitor of this enzyme (IC_{50}=7 nM) and a good chaperone molecule with a 1.8-fold increase of N370S mutant enzyme activity at 10 nM concentration.[6b] This compound was synthesized in ten steps and 6% overall yield from L-xylose.[6b] As this synthesis lacks reproducibility, we recently developed a different methodology to these iminosugars using the nucleophilic addition of Grignard reagents to the L-xylose-derived *N*-*tert*-butanesulfinyl imine.[7] However this ten-step synthesis leads to α-1-*C*-hexylimino-D-xylitol **2** (α-C_6-DIX, Fig. 1) with 4% overall yield and requires the use of expensive *tert*-butanesulfinamide.



1 2

Fig. 1. α-1-*C*-Alkyl imino-D-xylitol derivatives.

We describe here a more rapid and efficient methodology for the synthesis of α-1-*C*-alkyl-DIX, such as **1** and **2**, wherein the key step is the diastereoselective addition of allyltrimethylsilane to the

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N-benzyloxycarbonyl protected glycopyranosylamine derivative; we have already used this methodology for the synthesis of UDP-galactofuranose mimics.[8] While the synthesis of related iminosugar derivatives was reported to be successful by way of the addition of the allyl Grignard reagent to *N*-benzyl glycosylamines,[6e,9,†] a methodology originally pioneered by Nicotra and co-workers,[10] our approach has the definite advantage of avoiding *N*-protecting group replacement as the addition of AllylTMS to *N*–*Z* glycosylamines provides directly amino alditols derivatives in which nitrogen carries a deactivating protecting group. After cyclization, the allyl group can be rapidly functionalized by cross-metathesis, oxidation or other reactions with electrophilic reagents without further manipulation at the nitrogen atom. Moreover this synthetic strategy is also convenient for the preparation of functionalized 1-*C*-alkylated iminosugars in the L-*arabino* series, which might be, by analogy with the *xylo* series, potential pharmacological chaperones for mutant β-galactocerebrosidase (GALC). This enzyme hydrolyzes the glycosidic bond of galactosylceramide and psychosine (Fig. 2).

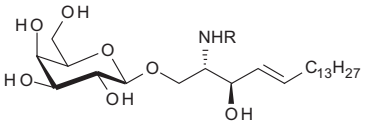


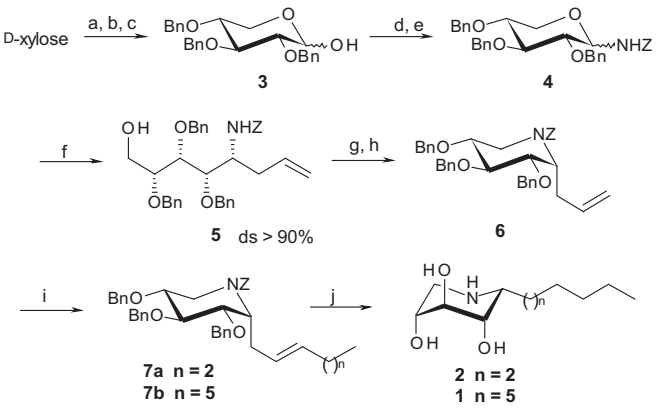
Fig. 2. Structures of galactosylceramide (R=$COC_{15}H_{31}$) and psychosine (R=H).

GALC deficiency is responsible for Krabbe disease, another LSD, which has currently no treatment available.[11] It has been shown very recently that PCT may also be a promising strategy for the treatment of this disease.[12]

2. Results and discussion

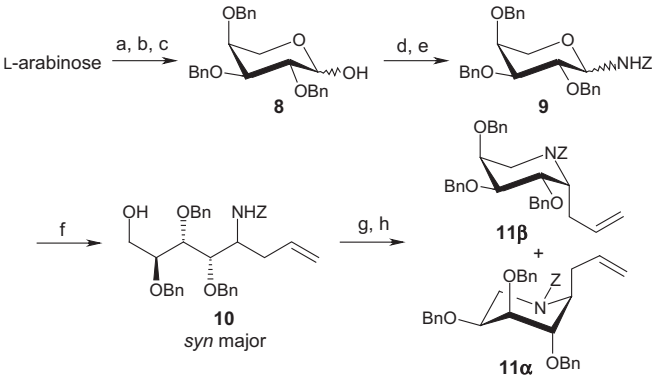
2,3,4-Tri-*O*-benzyl-D-xylopyranose **3** was easily synthesized from D-xylose in three steps and excellent overall yield.[13] Acetylation of the anomeric position followed by addition of benzyl carbamate in the presence of TMSOTf provided efficiently the *N*-protected xylopyranosylamine **4**. Using the conditions we developed for the synthesis of UDP-Gal*f* mimics,[8] this compound was then submitted to the addition of AllylTMS in the presence of TMSOTf leading to the open-chain amino D-iditol derivative **5**, in good yield (81%) and with very good *syn*-diastereoselectivity. Traces of two unseparable compounds (around 15%), one of which might be the other diastereoisomer, could be observed on the ^{1}H and ^{13}C NMR spectra. Fortunately these impurities were easily eliminated during the cyclization, which was efficiently achieved by mesylation of the free alcohol function, followed by a base-promoted ring closure giving the α-1-*C*-allyl imino-D-xylitol **6**. Its $^4C_1$ conformation was unambiguously established by the high ^{1}H NMR coupling constants between H3 and H2/H4 (J=9.3 Hz). The α configuration was also demonstrated by the $J_{1,2}$ coupling constant ($J_{1,2}$=5.9 Hz), although more definitive evidence comes from the NMR data of the final products **1** and **2**. Metathesis using second generation Hoveyda–Grubbs catalyst allowed chain elongation in moderate yield for (highly volatile) pentene and in good yield for octene. The iminosugars **6**, **7a**, and **7b** exist as mixtures of rotamers due to the presence of the benzyloxycarbonyl protective group. A last step of deprotection by hydrogenolysis provided quantitatively α-C_6-DIX **2** and α-C_9-DIX **1**. These iminosugars acting as potent GCase inhibitors were thus synthesized efficiently and reproducibly in ten steps and 11% and 20% overall yields, respectively, from a simple aldose (Scheme 1).

† Successful addition of allylindium to unprotected glycosylamines was recently reported.[9d]



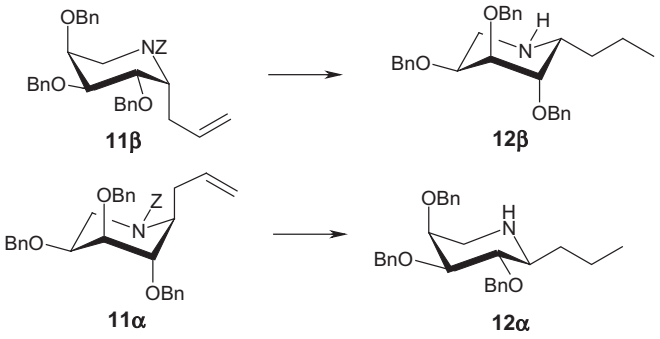
Scheme 1. Reagents and conditions: (a) MeOH, HCl (from $SOCl_2$), reflux (b) NaH, BnBr, TBAI, anhyd DMF, RT (c) 1 M H_2SO_4, AcOH, dioxane, reflux, 64% (3 steps) (d) Ac_2O, pyridine, RT (e) NH_2CO_2Bn, TMSOTf, anhyd CH_2Cl_2, 4 Å MS, RT, 85% (2 steps) (f) AllTMS, TMSOTf, anhyd CH_3CN, −20 °C, 81% (g) MsCl, NEt_3, anhyd CH_2Cl_2, 4 Å MS, RT (h) ^{t}BuOK, anhyd THF, RT, 59% (2 steps) (i) pent-1-ene (n=2), oct-1-ene (n=5), Hoveyda–Grubbs catalyst, anhyd CH_2Cl_2, RT, 41% (**7a**), 78% (**7b**) (j) H_2, Pd/C, 1 N HCl, ^{i}PrOH, RT, quant.

This methodology was found to be efficient also for the synthesis of iminosugars in the L-*arabino* series, which are galactoside mimics lacking the C5-CH_2OH group. 2,3,4-Tri-*O*-benzyl-L-arabinopyranose **8** was synthesized from L-arabinose using the same strategy as for xylose.[14] The *N*-protected arabinopyranosylamine derivative **9** was obtained by acetylation of the anomeric position followed by addition of benzyl carbamate in the presence of TMSOTf. Addition of AllylTMS gave the open-chain derivative **10** (mostly *syn*-diastereoisomer). Traces of the other diastereoisomer (around 10%) could be observed on ^{1}H and ^{13}C NMR spectra, but could not be separated from the desired compound at that stage of the synthesis. The mixture was then submitted to mesylation and cyclization under the same conditions as in *xylo* series, leading to a separable mixture of the two anomers **11β** and **11α**. The major one **11β** was thus obtained in eight steps and 13% overall yield (Scheme 2), which can be compared to the 26% overall yield obtained in the *xylo* series.



Scheme 2. Reagents and conditions: (a) MeOH, HCl (from AcCl), reflux, 59% (b) NaH, BnBr, anhyd DMF, RT (c) 3 N HCl, 80% aq AcOH, 90 °C, 56% (2 steps) (d) Ac_2O, pyridine, RT (e) NH_2CO_2Bn, TMSOTf, anhyd CH_2Cl_2, 4 Å MS, RT, 81% (2 steps) (f) AllTMS, TMSOTf, anhyd CH_3CN, −25 °C, 71% (g) MsCl, NEt_3, anhyd CH_2Cl_2, 4 Å MS, RT (h) ^{t}BuOK, anhyd THF, RT, 66% (**11β**), 8% (**11α**) (2 steps).

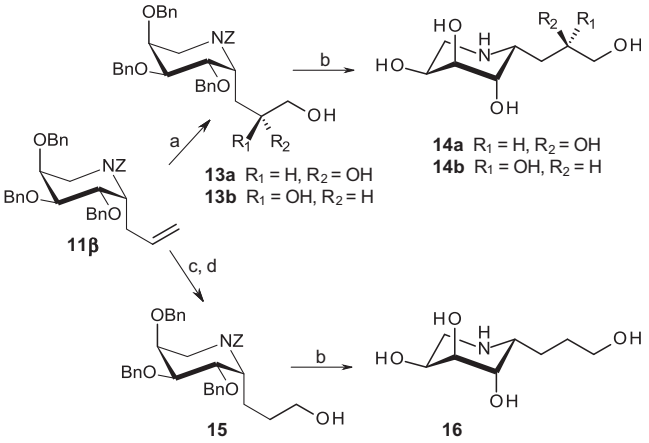
The low quality of ^{1}H NMR spectra due to the presence of rotamers did not allow the direct determination of the pseudo anomeric configurations of **11β** and **11α**. This was easily achieved on the nitrogen-deprotected iminosugars. For this purpose, compounds **12β** and **12α** were obtained by hydrogenolysis under basic conditions, in order to avoid *O*-debenzylation (Scheme 3). The pseudo anomeric configurations were assigned according to the small ^{1}H NMR coupling constants measured in **12β** ($J_{1,2}$=1.9 Hz, $J_{2,3}$=$J_{3,4}$=2.8 Hz), compared to the high ones measured in **12α**



Scheme 3. Reagents and conditions: H_2, Pd/C, NEt_3, ^{i}PrOH, RT, quant.

($J_{1,2}$=$J_{2,3}$=9.3 Hz). Inversion of conformation from **11β** ($^4C_1$) to **12β** ($^1C_4$) is consistent with the cleavage of the *N*-protecting group. *N*-Acyl-protected piperidines favor indeed a conformation in which the substituent α to nitrogen is in axial disposition.[15]

In order to prepare potential GALC inhibitors with a structure mimicking the functions present in psychosine (Fig. 2), we envisaged the synthesis of derivatives carrying a functionalized aglycone. So the allyl iminosugar **11β** was submitted to dihydroxylation on one hand and on the other, to hydroboration/oxidation reactions (Scheme 4).



Scheme 4. Reagents and conditions: (a) OsO_4, NMO, THF, ^{t}BuOH, H_2O, RT, 51% (**13a**), 22% (**13b**) (b) H_2, Pd/C, 1 N HCl, ^{i}PrOH, RT, 96% (**14a**), 57% (**14b**), quant. (**16**) (c) catecholborane, Wilkinson's catalyst, THF, 40 °C (d) NaOH, H_2O_2, RT, 46%.

Dihydroxylation was efficiently realized using the OsO_4/NMO system leading to a separable mixture of the two diastereoisomers **13a** and **13b**. Configuration of the secondary alcohol was determined by circular dichroism analysis. To assign the absolute configuration of the newly formed stereogenic center in compounds **13a** and **13b**, the in situ dimolybdenum methodology of electronic circular dichroism spectroscopy (ECD) has been applied. This straightforward, simple, and reliable approach consists of mixing a nonracemic transparent *vic*-diol with dimolybdenum tetraacetate acting as an auxiliary chromophore.[16] The transition metal ions, when complexed to an optically active ligand, become involved in the symmetry of the ligand. Thus, the Cotton Effects (CEs) related to electronic transitions of the metal atom are obtained and they are characteristic for the absolute configuration of the compound acting as ligand (in this case 1,2-diol). In general, an application of the helicity rule relating the sign of the O–C–C–O torsional angle with the sign of the CEs arising in the 300–400 nm spectral range allows an unequivocal assignment of the stereostructure of investigated diol units. This is due to the fact that in the chiral Mo-complexes formed in situ the conformational mobility of diols is very much reduced due to the restricted rotations of the remaining acetate ligands still coordinated to the metal atoms. Thus, this reduction or restriction of the conformational freedom makes an absolute configurational assignment possible on the basis of the chiroptical data alone. As can be seen in Fig. 3, a positive helicity of the diol **13a** correlates with positive CEs at 310 and 380 nm whilst the inverse correlation of helicity of the diol subunit and sign of CEs takes place for diol **13b**. Thus, provided the relative configuration of *vic*-diol after ligation to the Mo_2-core to be *gauche* with preferred antiperiplanar orientation of the hydroxyl group versus bulky substituent, the absolute configuration of the newly formed stereogenic center in **13a** is (*R*) and in **13b** (*S*).

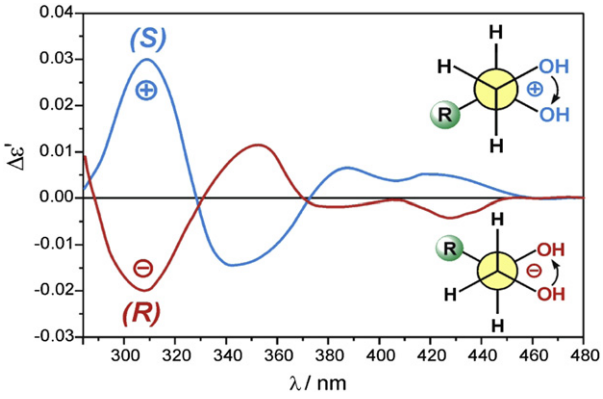


Fig. 3. ECD spectra of in situ formed Mo-complexes of **13a** (red line) and **13b** (blue line) recorded in DMSO. The preferred conformation of the diols in the chiral Mo-complexes is shown on the right.

Hydroboration/oxidation reaction was found to be more difficult. Using catecholborane and Wilkinson's catalyst,[17] compound **15** could be isolated only in moderate yield. Due to the presence of the benzyloxycarbonyl protective group, the iminosugars **13a**, **13b**, and **15** exist as mixtures of rotamers, which leads to broad signals on the ^{1}H NMR spectra. Finally, these compounds were submitted to hydrogenolysis leading to the L-*arabino* functionalized iminosugars **14a**, **14b**, and **16**. Evaluation of these compounds as inhibitors of lysosomal α-galactosidase, β-galactosidase and β-galactocerebrosidase is in progress to determine their activity and selectivity as potential pharmacological chaperones.

3. Conclusion

We improved the synthesis of 1-*C*-alkylated iminosugars in the D-xylopyranose series and demonstrated that this is also applicable in the L-arabinopyranose series. These compounds are potential pharmacological chaperones for the treatment of, respectively, Gaucher and Krabbe diseases. The key step is the diastereoselective addition of AllylTMS to *N*-*Z*-protected glycopyranosylamines, which is thus shown to be applicable not only to glycofuranosylamines.[8,18] This strategy allows the direct functionalization of the allyl substituent using metathesis or oxidation reactions, leading to a diversity of non-functionalized or functionalized 1-*C*-alkylated iminosugars.

4. Experimental section

4.1. General

All reactions requiring anhydrous conditions were carried out using oven-dried glassware under an atmosphere of dry Ar. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. CH_3CN was dried using activated 3 Å molecular sieves. All reagent-grade chemicals were obtained from commercial suppliers and were used as received. Infrared spectra were recorded using neat compounds on a Nicolet iS10 FT-IR spectrometer. Low-resolution

mass spectra were recorded on a Perkin–Elmer Sciex API 3000. High resolution mass spectra were recorded on a Bruker Q-TOF MaXis spectrometer in Orléans or on a Waters Q-TOF micro spectrometer in Clermont-Ferrand. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 250 or Bruker Avance 400 spectrometers. Chemical shifts are given in parts per million and are referenced to the residual solvent signal or to TMS as internal standard. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. ^{1}H and ^{13}C signals were attributed on the basis of H–H and C–H correlations. Specific optical rotations were measured at 20 °C in a 1-dm cell with a Perkin–Elmer 341 polarimeter. ECD spectra were acquired between 650 and 280 nm at room temperature with a Jasco J-815 spectropolarimeter using DMSO solutions in cells of 0.2 and 1 cm path length (spectral band width 2 nm, high sensitivity). Depending on the S/N-ratio the λ-scan speed was 200 nm/min. For ECD measurements the solid chiral diol (4.5–5 mg) was dissolved in a solution of the stock $[Mo_2(OAc)_4]$ complex (7–8 mg) in DMSO (10 mL) so that the molar ratio of the stock complex to diol was about 1:1.5. As the true concentrations of the individual optically active complexes are not known, apparent $\Delta\varepsilon'$ values are given, calculated from the total stock complex concentration and assuming 100% complexation. $[Mo_2(OAc)_4]$ and DMSO (Uvasol) were commercially available from Fluka AG and E. Merck, respectively, and were used without further purification. Analytical thin layer chromatography was performed using Silica Gel 60F_{254} precoated plates (Merck) with visualization by ultraviolet light and phosphomolybdic acid or ceric sulfate/ammonium molybdate solutions. Flash chromatography was performed on Silica Gel 60 (230–400 mesh).

4.2. Synthesis of 1-*C*-alkyl imino-D-xylitol derivatives

*4.2.1. N-Benzyloxycarbonyl 2,3,4-tri-O-benzyl-α,β-D-xylopyranosylamine (**4**).* To a solution of 2,3,4-tri-*O*-benzyl-α,β-D-xylofuranose **3** (6.0 g, 14.3 mmol) in pyridine (30 mL) was added Ac_2O (6.5 mL, 69.2 mmol, 4.8 equiv). The reaction mixture was stirred for 18 h at room temperature. CH_2Cl_2 was added (300 mL). The organic phase was washed with H_2O (3×400 mL) and dried over $MgSO_4$. After concentration under vacuum and coevaporation with toluene, the crude product was obtained as a colorless oil, which was used in the next step without further purification. 1-*O*-Acetyl 2,3,4-tri-*O*-benzyl-α,β-D-xylopyranose was dissolved in dry CH_2Cl_2 (30 mL) and stirred for 10 min under Ar in the presence of 4 Å molecular sieves and benzyl carbamate (4.3 g, 28.4 mmol, 2 equiv). TMSOTf (2.6 mL, 14.4 mmol, 1 equiv) was added and the mixture was stirred at room temperature for 1.5 h. NEt_3 (2.5 mL) was then added. The solid was filtered over Celite, washed with CH_2Cl_2 and the filtrate was concentrated under vacuum. Flash chromatography on silica gel (toluene/EtOAc 9:1) afforded the mixture of anomers (α/β 3:7) **4** (6.76 g, 85%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–7.24 (m, 20H, H_{Ar}), 5.80 (d, 0.3H, J=8.0 Hz, NH_α), 5.34 (dd, 0.3H, J=3.6, 8.0 Hz, $H1_\alpha$), 5.20 (br s, 0.7H, NH_β), 5.14–5.11 (m, 1.4H, $CO_2CH_2Ph_\beta$), 5.06–5.03 (m, 0.6H, $CO_2CH_2Ph_\alpha$), 4.91–4.48 (m, 6.7H, OCH_2Ph, $H1_\beta$), 3.90 (dd, 0.7H, J=5.1, 11.6 Hz, $H5b_\beta$), 3.78 (dd, 0.3H, J=3.9, 12.2 Hz, $H5b_\alpha$), 3.72–3.61 (m, 1.3H, H3, $H5a_\alpha$), 3.59–3.53 (m, 1H, $H2_\alpha$, $H4_\beta$), 3.45–3.41 (m, 0.3H, $H4_\alpha$), 3.32–3.22 (m, 1.4H, $H2_\beta$, $H5a_\beta$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.92, 155.63 (C=O), 138.46–136.14 (C_{Ar}), 128.57–127.79 (CH_{Ar}), 84.57 ($C3_\beta$), 82.17 ($C1_\beta$), 79.65 ($C2_\beta$), 77.83 ($C4_\beta$), 77.45 ($C1_\alpha$), 76.81 ($C3_\alpha$), 76.07 ($C2_\alpha$), 74.85 ($C4_\alpha$), 75.59–72.42 (OCH_2Ph), 67.15, 67.12 (CO_2CH_2Ph), 65.31 ($C5_\beta$), 62.50 ($C5_\alpha$). IR ν=3355, 3063, 3032, 2868, 1700, 1531, 1453, 1281, 1232, 1090, 1073, 1042, 731, 694. MS (ESI) m/z 576.5 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{34}H_{35}NNaO_6$ m/z 576.2362; found m/z 576.2357.

*4.2.2. 1-C-Allyl-2,3,4-tri-O-benzyl-1-(N-benzyloxycarbonyl)amino-1-deoxy-D-xylitol (**5**).* To a solution of **4** (6.67 g, 12.0 mmol) in dry CH_3CN (120 mL) under Ar at −20 °C was added AllylTMS (13 mL, 81.8 mmol, 6.8 equiv). After stirring for 15 min, TMSOTf (2.2 mL, 12.1 mmol, 1 equiv) was added and the reaction mixture was stirred for 20 h at −20 °C. At 0 °C, saturated $NaHCO_3$ (60 mL) was added. The mixture was diluted with EtOAc (300 mL) and H_2O (100 mL). The organic phase was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified twice by flash chromatography on silica gel (pet. ether/EtOAc 8:2) to afford **5** (5.78 g, 81%) as a colorless oil. ^{1}H NMR of the major diastereoisomer (400 MHz, $CDCl_3$): δ=7.34–7.28 (m, 20H, H_{Ar}), 5.63–5.52 (m, 1H, −CH=), 5.14 (d, 1H, J=10.0 Hz, NH), 5.06 (s, 2H, CO_2CH_2Ph), 4.99–4.93 (m, 2H, $=CH_2$), 4.88 (d, 1H, J=11.1 Hz, OCH_2Ph), 4.77 (d, 1H, J=11.2 Hz, OCH_2Ph), 4.68 (d, 1H, J=11.7 Hz, OCH_2Ph), 4.58 (d, 1H, J=11.2 Hz, OCH_2Ph), 4.52 (d, 1H, J=11.1 Hz, OCH_2Ph), 4.51 (d, 1H, J=11.7 Hz, OCH_2Ph), 3.82–3.65 (m, 6H, H1, H2, H3, H4, H5), 2.27–2.07 (m, 3H, $-CH_2-CH=$, OH). ^{13}C NMR of the major diastereoisomer (100 MHz, $CDCl_3$): δ=156.29 (C=O), 138.29–136.56 (C_{Ar}), 134.55 (−CH=), 128.64–127.82 (CH_{Ar}), 117.86 ($=CH_2$), 80.26, 79.80, 77.73 (C2, C3, C4), 75.23, 72.28 (OCH_2Ph), 66.86 (CO_2CH_2Ph), 61.41 (C5), 51.58 (C1), 38.05 ($-CH_2-CH=$). IR ν=3434, 3064, 3031, 2931, 2874, 1713, 1498, 1210, 1049, 1026, 734, 696. MS (ESI) m/z 618.5 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{41}NNaO_6$ m/z 618.2832; found m/z 618.2831.

*4.2.3. (1R)-1-C-Allyl-2,3,4-tri-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-xylitol (**6**).* To a solution of **5** (5.78 g, 9.70 mmol) in dry CH_2Cl_2 (100 mL) under Ar were added NEt_3 (3 mL, 21.5 mmol, 2.2 equiv) and 4 Å molecular sieves. The mixture was stirred for 10 min and MsCl (1.6 mL, 20.7 mmol, 2.1 equiv) was added. The reaction mixture was stirred for 23 h at room temperature. The solid was filtered, washed with CH_2Cl_2 (200 mL) and the filtrate was treated with saturated NH_4Cl (200 mL). The organic phase was washed with brine (200 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in dry THF (90 mL) under Ar and ^{t}BuOK (3.23 g, 28.8 mmol, 3 equiv) was added. The reaction mixture was stirred for 25 h at room temperature. Saturated NH_4Cl (200 mL) and EtOAc (300 mL) were added. The organic phase was washed with brine (200 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (toluene/EtOAc 98:2) afforded **6** (3.33 g, 59%) as a colorless oil and as a mixture of rotamers (A/B 1:1). $[\alpha]_D$ −15.1 (c=1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.25 (m, 20H, H_{Ar}), 5.76–5.66 (m, 0.5H, $-CH=_B$), 5.61–5.50 (m, 0.5H, $-CH=_A$), 5.14–4.92 (m, 4H, CO_2CH_2Ph, $=CH_2$), 4.89–4.81 (m, 2H, OCH_2Ph), 4.72–4.61 (m, 4.5H, OCH_2Ph, $H1_B$), 4.45–4.41 (m, 0.5H, $H1_A$), 4.41 (dd, 0.5H, J=5.7, 13.5 Hz, $H5_{eqA\ or\ B}$), 4.17 (dd, 0.5H, J=5.7, 13.5 Hz, $H5_{eqA\ or\ B}$), 3.68 (t, 1H, J=9.3 Hz, H3), 3.56 (dd, 0.5H, J=5.9, 9.3 Hz, $H2_B$), 3.50 (dd, 0.5H, J=5.9, 9.3 Hz, $H2_A$), 3.49–3.46 (m, 0.5H, $H4_{A\ or\ B}$), 3.41 (ddd, 0.5H, J=5.7, 9.3, 11.1 Hz, $H4_{A\ or\ B}$), 2.76 (dd, 0.5H, J=11.1, 13.5 Hz, $H5_{axA\ or\ B}$), 2.74 (dd, 0.5H, J=11.1, 13.5 Hz, $H5_{axA\ or\ B}$), 2.62–2.51 (m, 1H, $CH_2-CH=$), 2.35–2.25 (m, 1H, $CH_2-CH=$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.69, 155.60 (C=O), 138.93–136.56 (C_{Ar}), 134.54, 134.35 (−CH=), 128.63–127.69 (CH_{Ar}), 117.66, 117.41 ($=CH_2$), 82.20, 82.06 (C3), 79.81 (C2), 78.38, 78.34 (C4), 75.86–72.86 (OCH_2Ph), 67.60, 67.50 (CO_2CH_2Ph), 53.00, 52.28 (C1), 41.09, 40.81 (C5), 29.77, 29.73 ($-CH_2-CH=$). IR ν=3064, 3031, 2901, 2871, 1699, 1454, 1423, 1314, 1209, 1094, 734, 695. MS (ESI) m/z 600.5 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{39}NNaO_5$ m/z 600.2726; found m/z 600.2707.

*4.2.4. (1R)-2,3,4-Tri-O-benzyl-N-benzyloxycarbonyl-1-C-hex-2-enyl-1,5-dideoxy-1,5-imino-D-xylitol (**7a**).* To a solution of **6** (294 mg, 0.509 mmol) in dry CH_2Cl_2 (2 mL) under Ar were added second generation Hoveyda–Grubbs catalyst (20 mg, 0.032 mmol, 0.06 equiv) and pentene (720 μL, 6.57 mmol, 13 equiv). The reaction mixture was stirred for 30 h at 20 °C. The solvent was evaporated

and the crude product was purified twice by flash chromatography on silica gel (pet. ether/EtOAc 95:5) to afford **7a** (129 mg, 41%) as a colorless oil and as a mixture of rotamers (A/B 1:1). $[\alpha]_D$ −11.2 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=7.38–7.24 (m, 20H, H_{Ar}), 5.47–5.36 (m, 1H, −CH−CH_2−CH=C*H*), 5.33–5.26 (m, 0.5H, −CH−CH_2−C*H*=CH_B), 5.21–5.16 (m, 0.5H, −CH−CH_2−C*H*=CH_A), 5.13–5.01 (m, 2H, CO_2CH_2Ph), 4.89–4.81 (m, 2H, OCH_2Ph), 4.72–4.61 (m, 4.5H, OCH_2Ph, $H1_B$), 4.43–4.36 (m, 1H, $H1_A$, $H5_{eqA\ or\ B}$), 4.16 (dd, 0.5H, *J*=5.9, 13.6 Hz, $H5_{eqA\ or\ B}$), 3.72–3.65 (m, 1H, H3), 3.56 (dd, 0.5H, *J*=5.9, 9.5 Hz, $H2_B$), 3.50 (dd, 0.5H, *J*=5.9, 9.5 Hz, $H2_A$), 3.49–3.46 (m, 0.5H, $H4_{A\ or\ B}$), 3.41 (ddd, 0.5H, *J*=5.9, 8.8, 11.2 Hz, $H4_{A\ or\ B}$), 2.78–2.70 (m, 1H, $H5_{ax}$), 2.55–2.45 (m, 1H, −CH−C*H*$_2$−CH=), 2.29–2.19 (m, 1H, −CH−C*H*$_2$−CH=), 2.01–1.83 (m, 2H, −CH=CH−C*H*$_2$), 1.38–1.23 (m, 2H, −CH=CH−CH_2−C*H*$_2$), 0.83 (t, 3H, *J*=7.3 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.70, 155.55 (C=O), 138.95–136.66 (C_{Ar}), 133.63, 133.38 (−CH=CH−), 128.62–127.65 (CH_{Ar}), 125.72, 125.54 (−*C*H=CH−), 82.22, 82.07 (C3), 79.89 (C2), 78.41, 78.37 (C4), 75.83–72.73 (OCH_2Ph), 67.49, 67.42 (CO_2CH_2Ph), 53.29, 52.39 (C1), 41.04, 40.76 (C5), 34.75, 34.66 (=CH−CH_2−), 28.55, 28.42 (CH−CH_2−CH=), 22.64, 22.60 (=CH−CH_2−CH_2−), 13.76, 13.67 (CH_3). IR ν=3063, 3031, 2955, 2927, 2870, 1699, 1453, 1423, 1313, 1198, 1095, 733, 695. HRMS (ESI) $[M+Na]^+$ calcd for $C_{40}H_{45}NNaO_5$ *m*/*z* 642.3195; found *m*/*z* 642.3194.

*4.2.5. (1R)-2,3,4-Tri-O-benzyl-N-benzyloxycarbonyl-1-C-non-2-enyl-1,5-dideoxy-1,5-imino-D-xylitol (**7b**).* To a solution of **6** (89 mg, 0.154 mmol) in dry CH_2Cl_2 (4 mL) under Ar were added second generation Hoveyda–Grubbs catalyst (39 mg, 0.062 mmol, 0.4 equiv) and 1-octene (91 μL, 0.580 mmol, 3.8 equiv). The reaction mixture was stirred for 41 h at 40 °C. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (pet. ether/EtOAc 9:1) to afford **7b** (80 mg, 78%) as a colorless oil and as a mixture of rotamers (A/B 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ=7.38–7.24 (m, 20H, H_{Ar}), 5.48–5.39 (m, 1H, −CH−CH_2−CH=C*H*), 5.33–5.27 (m, 0.5H, −CH−CH_2−C*H*=CH_B), 5.21–5.15 (m, 0.5H, −CH−CH_2−C*H*=CH_A), 5.14–5.02 (m, 2H, CO_2CH_2Ph), 4.89–4.81 (m, 2H, OCH_2Ph), 4.72–4.61 (m, 4.5H, OCH_2Ph, $H1_B$), 4.42–4.36 (m, 1H, $H1_A$, $H5_{eqA\ or\ B}$), 4.16 (dd, 0.5H, *J*=5.6, 13.6 Hz, $H5_{eqA\ or\ B}$), 3.72–3.65 (m, 1H, H3), 3.56 (dd, 0.5H, *J*=6.0, 9.6 Hz, $H2_B$), 3.50 (dd, 0.5H, *J*=6.0, 9.6 Hz, $H2_A$), 3.47–3.37 (m, 1H, H4), 2.78–2.70 (m, 1H, $H5_{ax}$), 2.54–2.45 (m, 1H, −CH−C*H*$_2$−CH=), 2.29–2.19 (m, 1H, −CH−C*H*$_2$−CH=), 2.04–1.85 (m, 2H, −CH=CH−C*H*$_2$), 1.26–1.21 (m, 8H, CH_2), 0.90–0.85 (m, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.78, 155.65 (C=O), 139.04–136.76 (C_{Ar}), 133.98, 133.75 (−CH=*C*H−), 128.70–127.72 (CH_{Ar}), 125.51, 125.36 (−*C*H=CH−), 82.30, 82.15 (C3), 79.98 (C2), 78.50 (C4), 75.90–72.80 (OCH_2Ph), 67.56, 67.49 (CO_2CH_2Ph), 53.38, 52.49 (C1), 41.14, 40.86 (C5), 32.79, 32.73 (=CH−*C*H$_2$−), 31.94–29.00 (CH_2), 28.63, 28.51 (CH−*C*H$_2$−CH=), 22.83 (CH_2), 14.33 (CH_3). IR ν=3031, 2924, 2855, 1700, 1453, 1423, 1313, 1202, 1096, 968, 733, 695. HRMS (ESI) $[M+H]^+$ calcd for $C_{43}H_{52}NO_5$ *m*/*z* 662.384000; found *m*/*z* 662.383684.

*4.2.6. (1R)-1-C-Hexyl-1,5-dideoxy-1,5-imino-D-xylitol (**2**).* To a solution of **7a** (731 mg, 1.18 mmol) in ^{i}PrOH (10 mL) were added 1 N HCl (1.2 mL, 1 equiv) and 10% Pd/C (350 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere for 22 h. The catalyst was filtered through a membrane, washed with ^{i}PrOH and the filtrate was concentrated under vacuum. The residue was treated with Amberlite® IRA400 resin (OH^-) in water to give **2** (256 mg, quant.) as a white solid. $[\alpha]_D$ −21.3 (*c* 0.96, MeOH). Mp >145 °C (decomp.). ^1H NMR (400 MHz, MeOD): δ=3.87 (t, 1H, *J*=3.8 Hz, H3), 3.75–3.72 (m, 1H, H4), 3.69 (br s, 1H, H2), 3.21 (dd, 1H, *J*=2.2, 13.4 Hz, H5b), 3.12 (ddd, 1H, *J*=2.0, 6.2, 8.2 Hz, H1), 2.99 (dd, 1H, *J*=2.8, 13.4 Hz, H5a), 1.75–1.66 (m, 1H, −CH−C*H*$_2$−CH_2), 1.58–1.51 (m, 1H, −CH−C*H*$_2$−CH_2), 1.37–1.32 (m, 8H, CH_2), 0.91 (t, 3H, *J*=7.0 Hz, CH_3). ^{13}C NMR (100 MHz, MeOD): δ=70.56 (C2), 69.56 (C3), 69.36 (C4), 55.93 (C1), 47.36 (C5), 32.80, 30.31 (CH_2), 30.19 (CH−*C*H$_2$−CH_2), 26.42, 23.60 (CH_2), 14.41 (CH_3). IR ν=3363, 3281, 3091, 3018, 2925, 2856, 1539, 1460, 1416, 1292, 1054, 990, 723. HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{24}NO_3$ *m*/*z* 218.1756; found *m*/*z* 218.1767.

*4.2.7. (1R)-1-C-Nonyl-1,5-dideoxy-1,5-imino-D-xylitol (**1**).* To a solution of **7b** (53 mg, 0.080 mmol) in EtOH (2 mL) were added 1 N HCl (0.4 mL, 5 equiv) and 10% Pd/C (30 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere for 20 h. The catalyst was filtered through a membrane, washed with EtOH and the filtrate was concentrated under vacuum. The residue was treated with Amberlite® IRA400 resin (OH^-) in water to give **1** (21 mg, quant.) as a white solid. Analytical data are in accordance with the literature data.[6b]

4.3. Synthesis of 1-*C*-alkyl imino-L-arabinitol derivatives

*4.3.1. N-Benzyloxycarbonyl 2,3,4-tri-O-benzyl-α,β-L-arabinopyranosylamine (**9**).* To a solution of 2,3,4-tri-*O*-benzyl-α,β-L-arabinopyranose **8** (1.0 g, 2.38 mmol) in pyridine (4.8 mL) was added Ac_2O (1.2 mL, 12.8 mmol, 5.4 equiv). The reaction mixture was stirred for 3 h at room temperature. CH_2Cl_2 (48 mL) was added. The organic phase was washed with H_2O (3×18 mL) and dried over $MgSO_4$. After concentration under vacuum and coevaporation with toluene, the crude product was obtained as a colorless oil, which was used in the next step without further purification. 1-*O*-Acetyl 2,3,4-tri-*O*-benzyl-α,β-L-arabinopyranose was dissolved in dry CH_2Cl_2 (2.4 mL) containing 4 Å molecular sieves under Ar. After 5 min of stirring, benzyl carbamate (0.72 g, 4.76 mmol, 2 equiv), then TMSOTf (0.44 mL, 2.43 mmol, 1.0 equiv) were added. The mixture was stirred at room temperature for 2 h. NEt_3 (0.33 mL) was then added. The solid was filtered over Celite, washed with CH_2Cl_2 and the filtrate was concentrated under vacuum. Flash chromatography on silica gel (toluene/acetone 95:5) afforded the mixture of anomers (α/β 4:6) **9** (1.07 g, 81%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ=7.31–7.21 (m, 20H, H_{Ar}), 6.30 (d, 0.4H, *J*=6.7 Hz, NH_α), 5.68 (d, 0.6H, *J*=9.4 Hz, NH_β), 5.32 (d, 0.6H, *J*=9.4 Hz, $H1_\beta$), 5.18–5.15 (m, 0.4H, $H1_\alpha$), 5.15–5.03 (m, 2H, CO_2CH_2Ph), 4.73–4.34 (m, 6H, OCH_2Ph), 3.95–3.87 (m, 1H, H5b), 3.83–3.75 (m, 2.6H, H3, H4, $H5a_\beta$), 3.59 (t, 0.4H, *J*=5.3 Hz, $H2_\alpha$), 3.52 (dd, 0.4H, *J*=2.2, 11.6 Hz, $H5a_\alpha$), 3.47 (dd, 0.6H, *J*=1.9, 3.5 Hz, $H2_\beta$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.48 (C=O), 138.16–138.11 (C_{Ar}), 128.59–127.56 (CH_{Ar}), 79.04 ($C1_\alpha$), 77.60 ($C3_\alpha$), 76.98 ($C1_\beta$), 76.58 ($C2_\beta$), 76.20 ($C2_\alpha$), 73.10–72.93 (OCH_2Ph), 72.29–72.22 ($C3_\beta$, C4), 71.41, 71.39 (OCH_2Ph), 66.91, 66.79 (CO_2CH_2Ph), 62.57 ($C5_\beta$), 60.69 ($C5_\alpha$). IR ν=3320, 3063, 3031, 2902, 1732, 1689, 1534, 1292, 1250, 1081, 1045, 772, 730. MS (ESI) *m*/*z* 576.5 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{34}H_{35}NNaO_6$ *m*/*z* 576.2362; found *m*/*z* 576.2357.

*4.3.2. 1-C-Allyl-2,3,4-tri-O-benzyl-1-(N-benzyloxycarbonyl)amino-1-deoxy-L-arabinitol (**10**).* To a solution of **9** (1.07 g, 1.92 mmol) in dry CH_3CN (19 mL) under Ar at −20 °C was added AllylTMS (2.15 mL, 13.5 mmol; 7.0 equiv). After stirring for 10 min, TMSOTf (0.36 mL, 1.98 mmol; 1 equiv) was added and the reaction mixture was stirred overnight at −20 °C. At 0 °C, saturated $NaHCO_3$ (33 mL) was added. The mixture was diluted with EtOAc (200 mL). The organic phase was washed with brine (2×70 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (toluene/acetone 95:5) to afford **10** (0.82 g, 71%) as a colorless oil. ^1H NMR of the major diastereoisomer (400 MHz, $CDCl_3$): δ=7.32–7.23 (m, 20H, H_{Ar}), 5.73–5.63 (m, 1H, −CH=), 5.20 (d, 1H, *J*=9.8 Hz, NH), 5.13–5.05 (m, 4H, CO_2CH_2Ph, =CH_2), 4.87–4.44 (m, 6H, OCH_2Ph), 3.90–3.61 (m, 6H, H1, H2, H3, H4,

H5), 2.35–2.22 (m, 3H, CH_2–CH=, OH). ^{13}C NMR of the major diastereoisomer (100 MHz, $CDCl_3$): δ=156.28 (C=O), 138.44–136.62 (C_{Ar}), 134.51 (–CH=), 128.55–127.83 (CH_{Ar}), 118.21 (=CH_2), 80.81, 80.28, 79.42 (C2, C3, C4), 75.42, 75.27, 71.86 (OCH_2Ph), 66.97 (CO_2CH_2Ph), 61.34 (C5), 52.29 (C1), 38.21 (–CH_2–CH=). IR ν=3031, 2875, 1714.5, 1498, 1454, 1210, 1057, 1026.5, 734, 696. MS (ESI) *m/z* 618.0 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{41}NNaO_6$ *m/z* 618.2832; found *m/z* 618.2838.

*4.3.3. (1R)- and (1S)-1-C-Allyl-2,3,4-tri-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-L-arabinitol (**11β**) and (**11α**).* To a solution of **10** (0.82 g, 1.37 mmol) in dry CH_2Cl_2 (14 mL) under Ar were added NEt_3 (0.42 mL, 3.02 mmol, 2.2 equiv) and 4 Å molecular sieves. Then MsCl (0.22 mL, 2.84 mmol, 2.1 equiv) was added. The reaction mixture was stirred for 35 min at room temperature. The solid was filtered, washed with CH_2Cl_2 (150 mL) and the filtrate was treated with saturated NH_4Cl (27 mL). The organic phase was washed with brine (2×50 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in dry THF (14 mL) under Ar and ^{t}BuOK (0.31 g, 2.76 mmol, 2 equiv) was added. The reaction mixture was stirred for 2.5 h at room temperature. Saturated NH_4Cl (27 mL) and EtOAc (150 mL) were added. The organic phase was washed with brine (150 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (pet. ether/EtOAc 9:1) afforded **11β** (503 mg, 66%) and **11α** (61 mg, 8%) as colorless oils. **11β** was found to exist as a mixture of rotamers (A/B 1:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.00 (m, 20H, H_{Ar}), 5.74 (br s, 0.5H, –CH=$_B$), 5.60 (br s, 0.5H, –CH=$_A$), 5.14–5.07 (m, 2H, CO_2CH_2Ph), 5.03–4.91 (m, 2H, =CH_2), 4.85–4.46 (m, 7.5H, OCH_2Ph, H1, H5b$_{A\ or\ B}$), 4.31–4.20 (m, 0.5H, H5b$_{A\ or\ B}$), 4.12–4.07 (m, 1H, H2), 3.74–3.69 (m, 1H, H4), 3.55 (dd, 1H, *J*=3.3, 10.1 Hz, H3), 2.71 (br s, 1H, H5a), 2.58 (br s, 1H, CH_2–CH=), 2.22–2.13 (m, 1H, CH_2–CH=). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.23 (C=O), 138.77–136.77 (C_{Ar}), 135.09 (–CH=), 128.41–127.57 (CH_{Ar}), 117.12 (=CH_2), 78.26 (C3), 76.46 (C2), 73.27 (OCH_2Ph), 72.57 (C4), 72.31, 70.82 (OCH_2Ph), 67.45 (CO_2CH_2Ph), 53.63, 52.98 (C1), 40.03, 39.35 (C5), 29.37 (–CH_2–CH=). IR ν=3064, 3031, 2868, 1695, 1496, 1453, 1422, 1346, 1232, 1090, 1072, 1027, 967, 734, 695. MS (ESI) *m/z* 600.5 $[M+Na]^+$. HRMS (ESI) $[M+Na]^+$ calcd for $C_{37}H_{39}NNaO_5$ *m/z* 600.2726; found *m/z* 600.2712. **11α**: HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{40}NO_5$ *m/z* 578.29010; found *m/z* 578.29032.

*4.3.4. (1R)- and (1S)-2,3,4-Tri-O-benzyl-1-C-propyl-1,5-dideoxy-1,5-imino-L-arabinitol (**12β**) and (**12α**).* To a solution of **11β** or **11α** (60 mg, 0.104 mmol) in ^{i}PrOH (1 mL) were added NEt_3 (3.5 μL, 0.024 mmol, 0.24 equiv) and 10% Pd/C (15.6 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere for 2 h. The catalyst was filtered through a membrane, washed with CH_2Cl_2 and the filtrate was concentrated under vacuum to give, respectively, **12β** and **12α** (46 mg, quant.) as colorless oils. **12β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.17 (m, 15H, H_{Ar}), 4.78 (d, 1H, *J*=12.3 Hz, OCH_2Ph), 4.56 (d, 1H, *J*=12.3 Hz, OCH_2Ph), 4.55 (d, 1H, *J*=12.2 Hz, OCH_2Ph), 4.49 (d, 1H, *J*=12.2 Hz, OCH_2Ph), 4.43 (d, 1H, *J*=11.8 Hz, OCH_2Ph), 4.36 (d, 1H, *J*=11.8 Hz, OCH_2Ph), 3.86 (t, 1H, *J*=2.8 Hz, H3), 3.71 (ddd, 1H, *J*=2.8, 6.3, 9.3 Hz, H4), 3.37 (br d, 1H, *J*=2.8 Hz, H2), 3.04–2.97 (m, 2H, H5), 2.93 (dt, 1H, *J*=1.9, 6.9, 6.9 Hz, H1), 1.98 (br s, 1H, NH), 1.43–1.26 (m, 3H, CH_2–CH_2–CH_3), 1.20–1.10 (m, 1H, CH_2–CH_2–CH_3), 0.86 (t, 3H, *J*=7.3 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=139.05, 138.84, 138.36 (C_{Ar}), 128.46–127.65 (CH_{Ar}), 77.18 (C2), 75.11 (C4), 73.49 (C3), 73.13, 72.66, 71.05 (OCH_2Ph), 53.71 (C1), 44.58 (C5), 33.33 (CH_2–CH_2–CH_3), 19.72 (CH_2–CH_2–CH_3), 14.34 (CH_3). IR ν=3029, 2926, 2867, 1604, 1495, 1454, 1356, 1206, 1091, 1027, 909, 816, 733, 696. HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{36}NO_3$ *m/z* 446.26897; found *m/z* 446.26937. **12α**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.26 (m, 15H, H_{Ar}), 4.97 (d, 1H, *J*=10.8 Hz, OCH_2Ph), 4.70 (s, 2H, OCH_2Ph), 4.64–4.57 (m, 3H, OCH_2Ph), 3.77 (s, 1H, H4), 3.49–3.47 (m, 2H, H2, H3), 3.13 (dd, 1H, *J*=2.9, 14.3 Hz, H5b), 2.48–2.44 (m, 2H, H1, H5a), 2.00 (br s, 1H, NH), 1.88–1.81 (m, 1H, CH_2–CH_2–CH_3), 1.58–1.47 (m, 1H, CH_2–CH_2–CH_3), 1.36–1.23 (m, 2H, CH_2–CH_2–CH_3), 0.91 (t, 3H, *J*=7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.98, 138.73, 138.71 (C_{Ar}), 128.49–127.63 (CH_{Ar}), 84.36, 81.14 (C2, C3), 75.60 (OCH_2Ph), 73.83 (C4), 71.81, 71.51 (OCH_2Ph), 60.23 (C1), 47.06 (C5), 34.62 (CH_2–CH_2–CH_3), 19.22 (CH_2–CH_2–CH_3), 14.44 (CH_3). ^{1}H NMR (400 MHz, acetone-*d*6): δ=7.31–7.09 (m, 15H, H_{Ar}), 4.82 (d, 1H, *J*=11.2 Hz, OCH_2Ph), 4.60–4.53 (m, 3H, OCH_2Ph) 4.47 (d, 1H, *J*=11.2 Hz, OCH_2Ph), 4.46 (1H, *J*=11.8 Hz, OCH_2Ph), 3.81–3.80 (m, 1H, H4), 3.43 (dd, 1H, *J*=2.8, 9.3 Hz, H3), 3.29 (t, 1H, *J*=9.3 Hz, H2), 3.01 (dd, 1H, *J*=2.9, 14.4 Hz, H5b), 2.52 (br s, 1H, NH), 2.37 (dd, 1H, *J*=1.1, 14.4 Hz, H5a), 2.25 (dt, 1H, *J*=2.8, 9.3, 9.3 Hz, H1), 1.74–1.66 (m, 1H, CH_2–CH_2–CH_3), 1.48–1.37 (m, 1H, CH_2–CH_2–CH_3), 1.28–1.05 (m, 2H, CH_2–CH_2–CH_3), 0.84 (t, 2H, *J*=7.3 Hz, CH_3). ^{13}C NMR (100 MHz, acetone-*d*6): δ=140.52, 140.40, 140.20 (C_{Ar}), 129.00–127.96 (CH_{Ar}), 85.50 (C3), 82.03 (C2), 75.55 (OCH_2Ph), 75.39 (C4), 71.95, 71.73 (OCH_2Ph), 60.74 (C1), 47.61 (C5), 35.36 (CH_2–CH_2–CH_3), 19.94 (CH_2–CH_2–CH_3), 14.60 (CH_3). HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{36}NO_3$ *m/z* 446.26897; found *m/z* 446.26941.

*4.3.5. (1R)-2,3,4-Tri-O-benzyl-N-benzyloxycarbonyl-1-C-(2,3-dihydroxypropyl)-1,5-dideoxy-1,5-imino-L-arabinitol (**13**).* To a solution of **11β** (465 mg, 0.805 mmol) in a mixture of THF (3 mL), ^{t}BuOH (9 mL) and H_2O (1.6 mL) was added NMO (113 mg, 0.965 mmol, 1.2 equiv). After 5 min of stirring, a 2.5% solution of OsO_4 in ^{t}BuOH (0.82 mL, 0.062 mmol, 0.08 equiv) was added. The reaction was stirred at room temperature for 16 h. The mixture was then treated with a 0.1 N $Na_2S_2O_5$ solution (5 mL) and stirred for 30 min. CH_2Cl_2 (20 mL) and H_2O (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 9:1) to give a separable mixture of the two diastereoisomers **13a** (252 mg, 51%) and **13b** (106 mg, 22%) as colorless oils. **13a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.24 (m, 20H, H_{Ar}), 5.19 (d, 1H, *J*=12.2 Hz, CO_2CH_2Ph), 5.09 (d, 1H, *J*=12.2 Hz, CO_2CH_2Ph), 4.92–4.90 (m, 1H, H1), 4.73–4.55 (m, 6H, OCH_2Ph), 4.27 (d, 1H, *J*=14.6 Hz, H5b), 4.19 (dd, 1H, *J*=6.5, 10.0 Hz, H2), 3.97 (s, 1H, OH), 3.69 (s, 1H, H4), 3.53–3.49 (m, 4H, H3, C*H*OH, CH_2OH), 2.68 (d, 1H, *J*=14.6 Hz, H5a), 2.34–2.33 (m, 1H, OH), 1.89–1.82 (m, 1H, CH_2–CHOH–), 1.48 (t, 1H, *J*=13.1 Hz, CH_2–CHOH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.32 (C=O), 138.65–136.11 (C_{Ar}), 128.73–127.64 (CH_{Ar}), 78.40 (C3), 75.80 (C2), 73.31, 72.76 (OCH_2Ph), 72.48 (C4), 71.25 (OCH_2Ph), 68.28 (CO_2CH_2Ph), 68.25 (CHOH), 66.73 (CH_2OH), 50.41 (C1), 40.71 (C5), 27.85 (CH_2–CHOH–). HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{42}NO_7$ *m/z* 612.29558; found *m/z* 612.29541. **13b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.24 (m, 20H, H_{Ar}), 5.16–5.06 (m, 2H, CO_2CH_2Ph), 4.80 (d, 1H, *J*=11.4 Hz, OCH_2Ph), 4.73–4.49 (m, 6H, H1, OCH_2Ph), 4.28–4.25 (m, 1H, H5b), 4.12–4.09 (m, 1H, H2), 3.76–3.64 (m, 3H, C*H*OH, H4, CH_2OH), 3.51–3.44 (m, 2H, H3, CH_2OH), 2.86 (d, 1H, *J*=15.0 Hz, H5a), 2.04–2.00 (m, 1H, CH_2–CHOH–), 1.60–1.52 (m, 1H, CH_2–CHOH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.76 (C=O), 138.63–136.28 (C_{Ar}), 128.70–127.68 (CH_{Ar}), 78.42 (C3), 76.32 (C2), 73.61 (OCH_2Ph), 72.64, 72.61 (C4, CHOH), 71.44, 71.12 (OCH_2Ph), 68.02 (CO_2CH_2Ph), 66.29 (CH_2OH), 52.29 (C1), 40.79 (C5), 28.51 (CH_2–CHOH–). HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{42}NO_7$ *m/z* 612.29558; found *m/z* 612.29569.

*4.3.6. (1R)-1-C-((2R)-2,3-Dihydroxypropyl)-1,5-dideoxy-1,5-imino-L-arabinitol (**14a**).* To a solution of **13a** (213 mg, 0.348 mmol) in ^{i}PrOH (3.5 mL) were added 1 N HCl (0.7 mL, 2 equiv) and 10% Pd/C (52.5 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere overnight. The catalyst was filtered through a membrane, washed with MeOH and the filtrate was concentrated under vacuum. This procedure was repeated once to afford fully deprotected compound. The residue was treated with Amberlite® IRA400 resin (OH^-)

in water to give **14a** (69 mg, 96%) as a brown solid. $[\alpha]_D$ +10.3 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, MeOD): δ=3.87–3.85 (m, 1H, H3), 3.82 (dd, 1H, *J*=2.9, 7.9 Hz, H4), 3.78–3.72 (m, 1H, C*H*OH), 3.66 (dd, 1H, *J*=1.5, 3.9 Hz, H2), 3.50–3.43 (m, 2H, CH_2OH), 3.10–3.07 (m, 1H, H1), 2.76 (d, 2H, *J*=7.9 Hz, H5), 1.64–1.49 (m, 2H, CH_2–CHOH–). ^{13}C NMR (100 MHz, MeOD): δ=73.67 (C2), 72.60 (C3), 71.08 (CHOH), 67.71 (CH_2OH), 67.19 (C4), 51.67 (C1), 46.72 (C5), 36.46 (CH_2–CHOH–). HRMS (ESI) $[M+H]^+$ calcd for $C_8H_{18}NO_5$ *m*/*z* 208.11795; found *m*/*z* 208.11799.

*4.3.7. (1R)-1-C-((2S)-2,3-Dihydroxypropyl)-1,5-dideoxy-1,5-imino-L-arabinitol (**14b**).* To a solution of **13b** (103 mg, 0.168 mmol) in ^{i}PrOH (1.7 mL) were added 1 N HCl (0.34 mL, 2 equiv) and 10% Pd/C (25.5 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere overnight. The catalyst was filtered through a membrane, washed with MeOH and the filtrate was concentrated under vacuum. This procedure was repeated twice to afford fully deprotected compound. The residue was treated with Amberlite® IRA400 resin (OH^-) in water to give **14b** (20 mg, 57%) as a light yellow oil. $[\alpha]_D$ −11.3 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, MeOD): δ=3.89–3.86 (m, 1H, H3), 3.84 (dd, 1H, *J*=2.9, 7.9 Hz, H4), 3.81–3.75 (m, 1H, C*H*OH), 3.72–3.71 (m, 1H, H2), 3.51–3.43 (m, 2H, CH_2OH), 3.15–3.12 (m, 1H, H1), 2.79 (d, 2H, *J*=7.9 Hz, H5), 1.66 (ddd, 1H, *J*=3.3, 5.9, 14.2 Hz, CH_2–CHOH–), 1.53–1.46 (m, 1H, CH_2–CHOH–). ^{13}C NMR (100 MHz, MeOD): δ=72.53 (C3), 72.39 (C2), 71.91 (CHOH), 67.54 (CH_2OH), 67.16 (C4), 52.88 (C1), 46.79 (C5), 34.85 (CH_2–CHOH–). HRMS (ESI) $[M+H]^+$ calcd for $C_8H_{18}NO_5$ *m*/*z* 208.11795; found *m*/*z* 208.11787.

*4.3.8. (1R)-2,3,4-Tri-O-benzyl-N-benzyloxycarbonyl-1-C-(3-hydroxypropyl)-1,5-dideoxy-1,5-imino-L-arabinitol (**15**).* **11β** (208 mg, 0.360 mmol), catecholborane (1 N in THF, 0.72 mL, 2 equiv) and Wilkinson's catalyst (6.5 mg, 0.007 mmol, 0.02 equiv) were mixed under Ar. The reaction was heated at 40 °C for 4 days, then cooled down to room temperature and diluted with EtOH (0.72 mL). 2 N NaOH (0.72 mL) and 30% H_2O_2 (0.72 mL) were added. The reaction mixture was stirred at room temperature for 2.5 d. The aqueous phase was extracted with Et_2O (2×10 mL). The combined organic phases were washed with 0.1 N $Na_2S_2O_3$ (2×10 mL), 2 N NaOH (2×10 mL), H_2O (10 mL), saturated NH_4Cl (10 mL) and dried over $MgSO_4$. After concentration, the crude product was purified by flash chromatography on silica gel (pet. ether/EtOAc 8:2, then 5:5) to afford **15** (98 mg, 46%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.24 (m, 20H, H_{Ar}), 5.10 (br s, 2H, CO_2CH_2Ph), 4.79–4.24 (m, 8H, OCH_2Ph, H1, H5b), 4.09 (br s, 1H, H2), 3.73–3.53 (m, 3H, H4, CH_2OH), 3.55 (dd, 1H, *J*=2.8, 10.1 Hz, H3), 2.76–2.73 (m, 1H, H5a), 1.86–1.15 (m, 4H, CH_2–CH_2–CH_2OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.46 (C=O), 138.81–136.57 (C_{Ar}), 128.61–127.55 (CH_{Ar}), 78.30 (C3), 76.65 (C2), 73.29 (OCH_2Ph), 72.62 (C4), 72.26, 70.91 (OCH_2Ph), 67.70 (CO_2CH_2Ph), 62.62 (CH_2OH), 53.32 (C1), 40.00 (C5), 29.10, 20.58 (CH_2–CH_2–CH_2OH). HRMS (ESI) $[M+H]^+$ calcd for $C_{37}H_{42}NO_6$ *m*/*z* 596.30066; found *m*/*z* 596.30055.

*4.3.9. (1R)-1-C-(3-Hydroxypropyl)-1,5-dideoxy-1,5-imino-L-arabinitol (**16**).* To a solution of **15** (135 mg, 0.227 mmol) in ^{i}PrOH (0.44 mL) were added 1 N HCl (0.44 mL, 2 equiv) and 10% Pd/C (35 mg). The reaction mixture was stirred at room temperature under a H_2 atmosphere overnight. The catalyst was filtered through a membrane, washed with MeOH and the filtrate was concentrated under vacuum. This procedure was repeated once to afford fully deprotected compound. The residue was treated with Amberlite® IRA400 resin (OH^-) in water to give **16** (43 mg, quant.) as a light yellow oil. ^{1}H NMR (400 MHz, MeOD): δ=3.91–3.88 (m, 2H, H3, H4), 3.73–3.72 (m, 1H, H2), 3.58–3.56 (m, 2H, CH_2OH), 2.90 (t, 1H, *J*=6.3 Hz, H1), 2.81 (d, 2H, *J*=7.8 Hz, H5), 1.66–1.47 (m, 4H, CH_2–CH_2–CH_2OH). ^{13}C NMR (100 MHz, MeOD): δ=72.16 (C3 or C4), 71.49 (C2), 66.53 (C3 or C4), 62.91 (CH_2OH), 54.43 (C1), 46.39 (C5), 30.44, 28.20 (CH_2–CH_2–CH_2OH). HRMS (ESI) $[M+H]^+$ calcd for $C_8H_{18}NO_4$ *m*/*z* 192.12303; found *m*/*z* 192.12315.

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