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Looking glass inhibitors: both enantiomeric *N*-benzyl derivatives of 1,4-dideoxy-1,4-imino-D-lyxitol [a potent competitive inhibitor of α-D-galactosidase] and of 1,4-dideoxy-1,4-imino-L-lyxitol [a weak competitive inhibitor of α-D-galactosidase] inhibit naringinase, an α-L-rhamnosidase competitively

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ABSTRACT

Benzhydryl protection by diphenyldiazomethane of an alcohol in enantiomeric base-sensitive ribonolactones allows short efficient syntheses of 1,4-dideoxy-1,4-imino-D-lyxitol (DIL) and of 1,4-dideoxy-1,4-imino-L-lyxitol (LIL). DIL showed potent [K_i = 0.13 μM]—and LIL showed weak [K_i = 113 μM]—competitive inhibition of α-D-galactosidase. Both enantiomers *N*-benzyl-DIL [K_i = 64 μM] and *N*-benzyl-LIL [K_i = 13 μM] were moderate competitive inhibitors of naringinase, an α-L-rhamnosidase.

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1. Introduction

Herein, we report short syntheses of the enantiomers of 1,4-dideoxy-1,4-imino-D-lyxitol, DIL **1D** and LIL **1L**, in which the high yielding benzhydryl protection of the hydroxyl group by diphenyldiazomethane of enantiomeric base-sensitive ribonolactone acetonides **3D** and **3L** is a crucial step (Scheme 1). Both enantiomers **1D** and **1L** are competitive inhibitors of the coffee bean of α-D-galactosidase, whereas the corresponding *N*-benzyl derivatives **2D** and **2L** are competitive inhibitors of naringinase, an α-L-rhamnosidase.

Iminosugars, carbohydrate mimics in which the ring oxygen of a sugar is replaced by nitrogen, have considerable therapeutic potential.[1] Both the enantiomers of iminosugars frequently show potent inhibition of the same glycosidases.[2] Among the examples of inhibition by pyrrolidines as furanose analogues of hexoses,[3] the natural products DAB **4D** and DMDP **5D** are potent inhibitors of some α-glucosidases although both are moderate inhibitors of other glycosidases[4] (Scheme 2); however, their enantiomers LAB **4L**[5,6] and L-DMDP **5L**[7] are more specific and more potent inhibitors of α-glucosidases. Both the natural product casuarine **6D**[8] with six adjacent stereogenic centers and its enantiomer L-casuarine **6L**[9] display potent α-glucosidase inhibition with no significant inhibition of any other glycosidases. The synthetic mannofuranose mimic DIM **7D**[10] is an inhibitor of α-mannosidases; in contrast, its enantiomer L-DIM **7L**[11] is a potent inhibitor of nariginase, an α-L-rhamnosidase, and shows no inhibition of α-mannosidase. The natural product swainsonine **8D**[12] and many other mannofuranose analogues[13] are powerful inhibitors of α-mannosidase, but do not affect naringinase; L-swainsonine **8L**[14] is a highly potent and specific inhibitor of naringinase with no inhibition of mannosidases.[15] DAB-NAc **9D**, the *N*-acetylamino analogue of DAB **4D**, showed no inhibition of any glycosidase; in contrast LABNAc **9L** is the most potent pyrrolidine inhibitor of β-hexosaminidases yet described.[16]

2. Synthesis of DIL 1D and LIL 1L

Both enantiomers LIL **1L** and DIL **1D** have previously been made from carbohydrates,[17] amino acids,[18] or by asymmetric synthesis.[19] Although lactones are very powerful chirons, their base lability due to the acidic proton at C2 means that standard methods for *O*-benzyl protection do not reliably give good yields; although silyl ethers may easily be formed in sequences that require hydride reduction of the lactone, migration of the silyl ethers to the hydroxyl groups frequently causes complications. Protection of carbohydrate alcohols as the corresponding benzhydryl ethers by reaction with diazomethane,[20] a procedure that does not require any acid or base catalyst, is particularly suitable for lactones with an acidic proton at C2.[21] The present six-step syntheses of LIL **1L** and DIL **1D** from the readily available acetonides of

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Scheme 1. Synthesis of enantiomeric 1,4-dideoxy-1,4-imino-lyxitols **1D** and **1L**.

Scheme 2. Enantiomeric pyrrolidine glycosidase inhibition—potent inhibition implies μM K_i.

D-**3D**[22] and L-**3L**[23] ribonolactones, in overall yields of 22% and 19%, respectively, rely on the initial protection of the primary alcohol as the benzhydryl ether under neutral conditions.

For the synthesis of LIL **1L**, the acetonide of D-ribonolactone **3D** was heated at reflux with diphenyldiazomethane in acetonitrile to give the benzhydryl ether **10D** in 82% yield (Scheme 3). The reduction of the fully protected lactone **10D** with sodium borohydride in methanol afforded the diol **11D** (81% yield), which was esterified with mesyl chloride in pyridine to form the dimesylate **12D** in 93% yield. Treatment of dimesylate **12D** with benzylamine caused the initial displacement of the primary mesylate followed by intramolecular displacement of the secondary mesylate to give cyclization to the fully protected L-iminolyxitol **13L**. Dowex® 50WX8-100 (H^+ resin) in water caused hydrolysis of both the benzhydryl- and acetonide-protecting groups to give *N*-benzyl-LIL **2L** (55%) from which the benzyl group was removed by hydrogenolysis in the presence of palladium on carbon to give LIL **1L**, isolated as its crystalline hydrochloride in 76% yield [22% overall yield from the D-ribonolactone **3D**]. Enantiomer DIL **1D** was prepared by an identical sequence from L-ribonolactone **3L** in an overall yield of 19%.

3. Glycosidase inhibition

DIL **1D** and LIL **1L**, and their *N*-benzyl analogues **2D** and **2L** were assayed as glycosidase inhibitors against a range of enzymes (Table 1).

This work confirms the original claim[5] that DIL **1D** is a potent α-D-galactosidase inhibitor, but is a much weaker inhibitor of α-D-mannosidase than DIM **7D**. The pyranose analogue of galactose, DGJ **14D**, with IC_{50} 0.003 μM (Fig. 1) is around 1000 times more potent that its enantiomer L-DGJ **14L** (IC_{50} 13 μM);[2c] DIL **1D**, the

Scheme 3. Reagents and conditions: (i) Ph_2CN_2, MeCN, 82% [81%*]; (ii) $NaBH_4$, MeOH, 81% [78%*]; (iii) $MeSO_2Cl$, pyridine, 93% [100%*]; (iv) $PhCH_2NH_2$, 86% [95%*]; (v) 1,4-dioxane:H_2O. 1:1, Dowex, 55% [43%*]; (vi) H_2, Pd, 1,4-dioxane;and then aq HCl, 76% [75%*]. [*] are yields obtained for the enantiomeric series starting from **3L** to give **1D**.

Table 1
Concentration of iminosugars giving 50% inhibition of glycosidases [with K_i of potent inhibitors]

IC_{50} (μM) Enzyme	**1D**	**1L**	**2D**	**2L**
α-Glucosidase				
Rice	845	302	NI (45.4%)	NI (0%)
Yeast	NI[a] (12.3%)[b]	331	NI (19.7%)	NI (3.1%)
β-Glucosidase				
Almond	329	443	NI (10.5%)	NI (9.5%)
Bovine liver	NI (22.1%)	NI (18.3%)	NI (1.0%)	NI (37.3%)
α-Galactosidase				
Coffee beans	**0.5 K_i = 0.13 μM**	**209 K_i = 113 μM**	125	NI (11.6%)
β-Galactosidase				
Bovine liver	NI (3.0%)	NI (28.9%)	NI (0%)	NI (22.6%)
α-Mannosidase				
Jack bean	39	677	NI (15.0%)	NI (0%)
β-Mannosidase				
Snail	NI (1.3%)	NI (19.6%)	NI (0%)	NI (1.6%)
α-L-Fucosidase				
Bovine epididymis	98	80	NI (31.1%)	NI (38.1%)
α-L-Rhamnosidase				
P. decumbens	NI (10.9%)	340	**83 K_i = 64 μM**	**21 K_i = 13 μM**
β-Glucuronidase				
E. coli	NI (0%)	NI (43.6%)	NI (0%)	NI (43.8%)
Bovine liver	NI (26.1%)	NI (43.6%)	NI (19.4%)	NI (0%)
β-*N*-Acetylglucosaminidase				
Jack bean	364	NI (42.4%)	NI (14.2%)	NI (28.6%)
Bovine kidney	NI (43.9%)	NI (29.7%)	NI (14.3%)	NI (21.2%)
β-Xylosidase				
Aspergillus niger	NI (13.0%)	NI (3.4%)	NI (2.1%)	NI (3.3%)

[a] NI: no inhibition (less than 50% inhibition at 1000 μM).
[b] ( ): Inhibition% at 1000 μM.

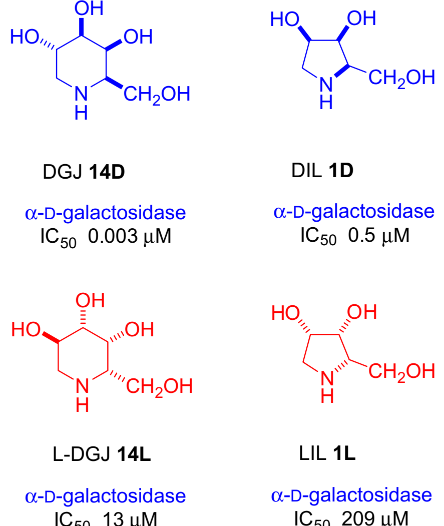

Figure 1. Enantiomeric piperidine and pyrrolidine α-D-galactosidase inhibition.

most potent furanose inhibitor yet described with IC_{50} 0.5 μM, is much more potent than the enantiomer LIL **1L** (IC_{50} 209 μM). Both **1D** and **1L** are competitive inhibitors of coffee bean α-D-galactosidase as shown by the Lineweaver–Burk plots (Fig. 2) and moderate inhibitors of bovine epididymis α-L-fucosidase [DIL **1D** IC_{50} 98 μM; LIL **1L** IC_{50} 80 μM].

Both *N*-benzyl-DIL **2D** [K_i = 64 μM] and *N*-benzyl-LIL **2L** [K_i = 13 μM] were moderate competitive inhibitors of naringinase, an α-L-rhamnosidase; the structural relation between **2D** and **2L** and L-swainsonine **8L** is shown in Figure 3. However, neither *N*-benzyl derivative showed any significant inhibition of α-D-galactosidase. It is well established that N-alkylation of iminosugars may have significant modifications in the potency and specificity of the inhibition of glycosidases.[1,24] This example of a change of specificity of enzyme inhibition by N-alkylation is very rare.

4. Conclusion

Benzhydryl protection of the readily available enantiomeric acetonides **3L** and **3D** is a key step in the efficient syntheses of the iminolyxitols DIL **1D** and LIL **1L**. Compound DIL **1D** was shown to be the most potent simple pyrrolidine inhibitor of α-D-galactosidase. Both enantiomeric *N*-benzyl iminolyxitols **2D** and **2L** have no significant α-D-galactosidase inhibition but both are moderate inhibitors of α-L-rhamnosidase; such a change in enzyme inhibition by N-alkylation is almost unprecedented.

5. Experimental

All commercial reagents were used as supplied. Tetrahydrofuran was purchased dry from the Aldrich chemical company in Sure-Seal™ bottles. Pyridine was purchased dry from the Aldrich chemical company in Sure-Seal™ bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC

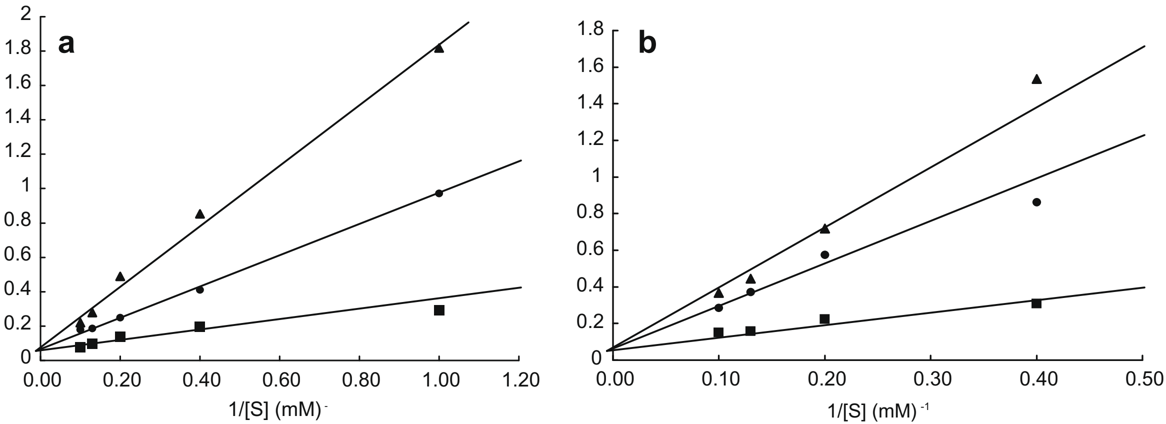

Figure 2. Lineweaver–Burk plots showing competitive α-D-galactosidase inhibition by (a) DIL **1D** and (b) LIL **2D;** (a) Concd DIL **1D**: 0 (■), 0.5 μM (●), 1 μM (▲) K_i = 0.13 μM. (b) Concd LIL **1L**: 0 (■), 250 μM (●), 500 μM (▲) K_i = 141 μM.

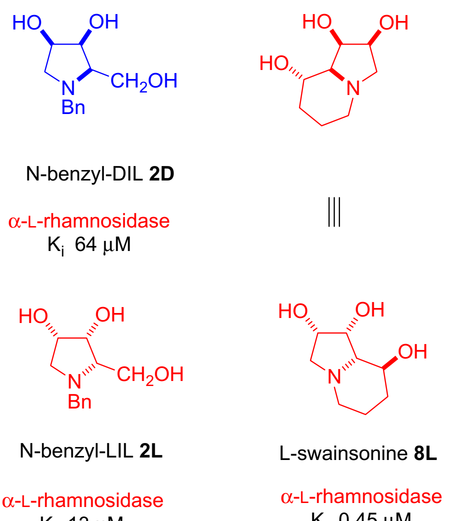

Figure 3. Enantiomeric pyrrolidine α-L-rhamnosidase inhibition.

grade), without prior purification. Reactions performed under an atmosphere of argon or hydrogen gas were maintained by an inflated balloon. All solutions are saturated unless otherwise stated. 'Dowex' refers to Dowex® 50WX8-100 (H^+ resin). Thin layer chromatography (TLC analysis) was performed on aluminum sheets coated with 60 F_{254} silica supplied by Merck. Sheets were visualized using a spray of either 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid, or potassium permanganate (0.5% in 1 M NaOH). Flash chromatography was performed either on Sorbsil C60 40/60 silica or on Merck grade 9385, 230–400 mesh, 60 Å. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 mL^{-1}. Infrared spectra were recorded on a Bruker Tensor 27 FT IR spectrophotometer using thin films on either NaCl or Ge plates. Only the characteristic peaks are quoted. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) or a Bruker AV400 (^{1}H: 400.2 MHz and ^{13}C: 100.6 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (J) in hertz (Hz). Residual signals from the solvents were used as an internal reference. 1, 4-Dioxane was used as an internal reference where D_2O is used as the solvent. Low resolution mass spectra (m/z) were recorded on a Micromass LCT (ESI) spectrometer. High resolution mass spectra (HRMS m/z) were carried out on a Bruker MicroTof (resolution = 10,000 FWHM). Electrospray (ESI) was used throughout. Assays for the inhibition of glycosidases were performed as previously described.[11]

5.1. 5-*O*-Benzhydryl-2,3-*O*-isopropylidene-D-ribono-1,4-lactone 10D

Diphenyldiazomethane (1.61 g, 8.29 mmol) was added to a stirred solution of the acetonide of D-ribonolactone **3D** (1.04 g, 5.53 mmol) in acetonitrile (55 mL) and the reaction mixture was heated at reflux for 6 h. TLC analysis (2:1, cyclohexane/ethyl acetate) showed a significant residual starting material (R_f 0.2) and a major product (R_f 0.6). An additional equivalent of diphenyldiazomethane (1.07 g, 5.53 mmol) was added and the reaction was heated at reflux for a further 6 h, after which time TLC analysis indicated that only trace starting material remained. The reaction mixture was concentrated in vacuo and the resulting residue purified by column chromatography (cyclohexane/ethyl acetate, 20:1→5:1) to give the fully protected lactone **10D** (1.60 g, 82%) as a yellow–orange oil. HRMS (ESI+ve): found: 377.1359 $[M+Na]^+$, $C_{21}H_{22}NaO_5$ requires: 377.1365; $[\alpha]_D^{23} = -23.5$ (c 0.81, $CHCl_3$); ν_{max} (thin film): 1786 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 1.38 (3H, s, C(CH_3)$_2$), 1.49 (3H, s, C(CH_3)$_2$), 3.65 (1H, dd, H5, $J_{5,4}$ 1.7, J_{gem} 10.6), 3.76 (1H, dd, H5′, $J_{5',4}$ 1.7, J_{gem} 10.6), 4.67 (1H, a-t, H4, J 1.9), 4.76 (1H, d, H3, $J_{3,2}$ 5.5), 4.87 (1H, d, H2, $J_{2,3}$ 5.5), 5.37 (1H, s, Ph_2CH), 7.22–7.42 (10H, m, Ph_2CH); δ_C ($CDCl_3$, 100.6 MHz): 25.7, 26.8 (C(CH_3)$_2$), 68.0 (C5), 75.8 (C2), 78.5 (C3), 81.1 (C4), 84.8 (Ph_2CH), 113.2 (C(CH_3)$_2$), 126.7, 126.8, 127.9, 128.0, 128.6, 128.7 (Ph_2CH), 140.6, 141.0 ($ArC_{quat.}$), 174.4 (C1); LRMS (ESI+ve): m/z (%) 372 (100) $[M+NH_4]^+$.

For the enantiomer **10L**, 81%, yellow oil, $[\alpha]_D^{21} = +20.8$ (c 1.0, $CHCl_3$).

5.2. 5-*O*-Benzhydryl-2,3-*O*-isopropylidene-D-ribitol 11D

Sodium borohydride (51 mg, 1.35 mmol) was added to a solution of benzhydryl lactone **10D** (479 mg, 1.35 mmol) in methanol (10 mL) at 0 °C and the reaction mixture was stirred at room temperature. The reaction was monitored hourly by TLC analysis (1:1, cyclohexane/ethyl acetate); four further additions of 1.35 mmol of sodium borohydride were required to bring the reaction to completion, with one addition per hour. The starting material (R_f 0.8) was no longer present, with a strong product spot clearly visible (R_f 0.5). The reaction mixture was neutralized with ammonium

chloride (satd, aq), concentrated in vacuo, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 2:1) to yield the diol **11D** (393 mg, 81%) as an off-white solid. HRMS (ESI+ve): found: 381.1666 $[M+Na]^+$, $C_{21}H_{26}NaO_5$ requires: 381.1678; mp 90–92 °C; $[\alpha]_D^{23} = +42.2$ (c 0.39, $CHCl_3$); ν_{max} (thin film): 3416 (s, br, OH); δ_H ($CDCl_3$, 400 MHz): 1.33 (3H, s, $C(CH_3)_2$), 1.36 (3H, s, $C(CH_3)_2$), 3.58–3.63 (2H, br, s, 1-OH, 4-OH), 3.61 (1H, dd, H5, $J_{5,4}$ 6.5, J_{gem} 9.9), 3.74–3.78 (1H, dd, H1, $J_{1,2}$ 5.4, J_{gem} 11.3), 3.77–3.80 (1H, dd, H5′, $J_{5',4}$ 2.7, J_{gem} 9.8), 3.86–3.92 (1H, dd, H1′, $J_{1',2}$ 7.7, J_{gem} 11.4), 3.99–4.04 (1H, ddd, H4, $J_{4,5'}$ 2.7, $J_{4,5}$ 6.8, $J_{4,3}$ 9.6), 4.13 (1H, dd, H3, $J_{3,2}$ 5.9, $J_{3,4}$ 9.7), 4.37 (1H, a-dt, H2, J 5.5, $J_{2,1'}$ 7.6), 5.44 (1H, s, Ph_2CH), 7.22–7.36 (10H, m, Ph_2CH); δ_C ($CDCl_3$, 100.6 MHz): 25.2, 27.8 ($C(CH_3)_2$), 60.8 (C1), 68.9 (C4), 70.6 (C5), 77.2 (C2), 77.5 (C3), 84.3 (Ph_2CH), 108.6 ($C(CH_3)_2$), 126.9, 127.8, 128.5, 128.5 (Ph_2CH), 141.5, 141.5 (ArC_{quat}); LRMS (ESI-ve): m/z (%) 358 (100), $[M-H]^-$, 404 (85) $[M+EtO]^-$.

For the enantiomer **11L**, 78%, mp 90–92 °C; $[\alpha]_D^{21} = -27.7$ (c, 1.0 in $CHCl_3$).

5.3. 5-*O*-Benzhydryl-2,3-*O*-isopropylidene-1,4-di-*O*-methanesulfonyl-D-ribitol 12D

Methanesulfonyl chloride (0.36 mL, 4.64 mmol) was added to a solution of the protected diol **11D** (664 mg, 1.85 mmol) in anhydrous pyridine (13 mL) and cooled to 0 °C; the reaction was stirred at room temperature for 2.5 h. TLC analysis (2:1, cyclohexane/ethyl acetate) showed the conversion of starting material (R_f 0.24, staining blue) to one major product (R_f 0.33, staining yellow). Pyridine was removed in vacuo, and the resulting residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:1) to give dimesylate **12D** (884 mg, 93%) as a colorless oil. HRMS (ESI+ve): found: 537.1218 $[M+Na]^+$, $C_{23}H_{30}NaS_2O_9$ requires: 537.1229; $[\alpha]_D^{23} = -21.7$ (c 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 1.36 (3H, s, $C(CH_3)_2$), 1.44 (3H, s, $C(CH_3)_2$), 3.03 (6H, s, 2 × $-OSO_2CH_3$), 3.77 (1H, dd, H5, $J_{5,4}$ 5.1, J_{gem} 11.5), 3.88 (1H, dd, H5′, $J_{5',4}$ 2.6, J_{gem} 11.4), 4.36 (1H, dd, H1, $J_{1,2}$ 6.8, J_{gem} 10.4), 4.42 (1H, dd, H3, $J_{3,2}$ 5.8, $J_{3,4}$ 6.8), 4.48 (1H, m, H2), 4.53 (1H, dd, H1′, $J_{1',2}$ 3.4, J_{gem} 10.5), 4.97–5.01 (1H, ddd, H4, $J_{4,5}$ 2.4, $J_{4,5'}$ 4.9, $J_{4,3}$ 7.0), 5.43 (1H, s, Ph_2CH), 7.22–7.36 (10H, m, Ph_2CH); δ_C ($CDCl_3$, 100.6 MHz): 25.4, 27.5 ($C(CH_3)_2$), 37.4, 39.2 (2 × $-OSO_2CH_3$), 68.2 (C1), 68.4 (C5), 74.6 (C2), 75.1 (C3), 78.2 (C4), 84.6 (Ph_2CH), 109.6 ($C(CH_3)_2$), 126.9, 127.0, 127.9, 127.9, 128.6, 128.6 (Ph_2CH), 133.8, 133.8 (ArC_{quat}); LRMS (ESI+ve): m/z (%) 532 (100), $[M+NH_4]^+$, 537 (80) $[M+Na]^+$.

For the enantiomer **12L**, 100%, colorless oil, $[\alpha]_D^{23} = +20.2$ (c 0.98, $CHCl_3$).

5.4. 5-*O*-Benzhydryl-*N*-benzyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-imino-L-lyxitol 13L

A stirred solution of the dimesylate **12D** (179 mg, 0.35 mmol) in benzylamine (5 mL) was heated at reflux for 18 h. After this time TLC analysis (2:1, cyclohexane/ethyl acetate) showed conversion of the starting material (R_f 0.3) to one major product (R_f 0.8). The solution was concentrated in vacuo by co-evaporation with toluene; the residue was purified by column chromatography (cyclohexane/ethyl acetate, 40:1→27:1) to give the protected 1,4-imino-L-lyxitol **13L** (129 mg, 86%) as a yellow oil. HRMS (ESI+ve): found: 430.2377 $[M+H]^+$, $C_{28}H_{32}NO_3$ requires: 430.2382; $[\alpha]_D^{23} = +64.0$ (c 0.75, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 1.32 (3H, s, $C(CH_3)_2$), 1.48 (3H, s, $C(CH_3)_2$), 2.05 (1H, dd, H1, $J_{1,2}$ 4.6, J_{gem} 11.2), 2.62 (1H, a-q, H4, J 5.2), 3.03 (1H, d, H1′, J_{gem} 11.2), 3.26 (1H, d, $PhCH_2$, J_{gem} 13.7), 3.74 (1H, dd, H5, $J_{5,4}$ 5.6, J_{gem} 9.7), 3.90 (1H, dd, H5′, $J_{5',4}$ 5.4, J_{gem} 9.8), 4.28 (1H, d, $PhCH_2'$, J_{gem} 13.7), 4.59 (1H, dd, H2, $J_{2,1}$ 4.8, $J_{2,3}$ 6.3), 4.71 (1H, dd, H3, $J_{3,4}$ 5.0, $J_{3,2}$ 6.3), 5.42 (1H, s, Ph_2CH), 7.21–7.50 (15H, m, Ph_2CH, $PhCH_2$); δ_C ($CDCl_3$, 100.6 MHz): 25.7, 26.3 ($C(CH_3)_2$), 57.8 ($PhCH_2$), 59.6 (C1), 67.2 (C4), 68.4 (C5), 78.1 (C2), 81.1 (C3), 84.3 (Ph_2CH), 111.2 ($C(CH_3)_2$), 126.7, 127.0, 127.1, 127.3, 127.4, 128.1, 128.3, 128.4, 128.7 (Ph_2CH, $PhCH_2$), 142.3, 142.3, 138.8 (ArC_{quat}); LRMS (ESI+ve): m/z (%) 430 (100), $[M+H]^+$, 452 (46) $[M+Na]^+$.

For the enantiomer **13D**, 95%, yellow oil, $[\alpha]_D^{20} = -65.6$ (c 0.99, $CHCl_3$).

5.5. *N*-Benzyl-1,4-dideoxy-1,4-imino-L-lyxitol 2L

A solution of the protected iminolyxitol **13L** (270 mg, 0.63 mmol) in 1,4-dioxane (1 mL) and water (1 mL) was stirred for 18 h at room temperature with Dowex. TLC analysis (3:1, cyclohexane/ethyl acetate) after this time showed that no starting material remained (R_f 0.7). The resin was filtered off and washed with methanol, and then separately with 2 M ammonia (aq) (2 × 10 mL). The filtrate was concentrated in vacuo to give *N*-benzyl-L-imino-lyxitol **2L** (77 mg, 55%), orange oil. HRMS (ESI+ve): found: 224.1281 $[M+H]^+$, $C_{12}H_{18}NO_3$ requires: 224.1287; $[\alpha]_D^{22} = +46.6$ (c 1.0, H_2O); ν_{max} (thin film): 3385 (s, br, OH); δ_H (D_2O, 400 MHz): 2.66 (1H, dd, H1, $J_{1,2}$ 6.3, J_{gem} 11.6), 2.67 (1H, dd, H1′, $J_{1',2}$ 5.3, J_{gem} 11.6), 2.82 (1H, ddd, H4, $J_{4,5}$ 4.4, $J_{4,3}$ 5.9, $J_{4,5'}$ 7.4), 3.44 (1H, dd, H5, $J_{5',4}$ 4.3, J_{gem} 11.0), 3.47 (1H, d, $PhCH_2$, J_{gem} 12.8), 3.62 (1H, dd, H5′, $J_{5',4}$ 7.5, J_{gem} 11.1), 3.75 (1H, d, $PhCH_2$, J_{gem} 12.8), 4.06 (1H, a–q, H2, J 5.6), 4.14 (1H, dd, H3, $J_{3,2}$ 5.0, $J_{3,4}$ 5.8), 7.22–7.30 (5H, m $PhCH_2$); δ_C (D_2O, 100.6 MHz): 56.8 (C1), 59.45, 59.52 ($PhCH_2$, C5), 66.4 (C4), 70.1 (C2), 71.9 (C3), 128.1, 128.9, 130.3 ($PhCH_2$), 137.5 (ArC_{quat}); LRMS (ESI-ve): m/z (%) 222 (100) $[M-H]^-$, 282 (96) $[M+AcO]^-$.

For the enantiomer **2D**, 43%, yellow oil, $[\alpha]_D^{21} = -46.2$ (c 1.0, H_2O).

5.6. 1,4-Dideoxy-1,4-imino-L-lyxitol 1L

A solution of *N*-benzyl-L-imino-lyxitol **2L** (65 mg, 0.29 mmol) in 1,4-dioxane (1 mL) in the presence of 10% palladium on carbon (6 mg, 10% by weight) was stirred at room temperature under a hydrogen atmosphere for 18 h. TLC analysis (9:1, ethyl acetate/methanol) showed the complete consumption of starting material (R_f 0.3) and a single product (R_f 0.0). The reaction mixture was filtered through Celite®, the filtrate was concentrated in vacuo, and treated with aqueous 2 M hydrochloric acid (aq). Concentration in vacuo yielded the hydrochloride of L-imino-lyxitol **1L**.HCl salt (30 mg, 76%) as a white crystalline solid. HRMS (ESI+ve): found: 134.0812 $[M+H]^+$, $C_5H_{12}NO_3$ requires: 134.0817; mp 153–154 °C; $[\alpha]_D^{24} = -20.7$ (c 0.60, H_2O) (lit.[25] $[\alpha]_D^{20} = -13.2$ (c 0.014, H_2O)); ν_{max} (thin film): 3385 (s, br, OH); δ_H (D_2O, 400 MHz): 2.85 (1H, dd, H1, $J_{1,2}$ 7.3, J_{gem} 11.8), 3.18 (1H, dd, H1′, $J_{1',2}$ 7.3, J_{gem} 11.8), 3.34–3.39 (1H, m, H4), 3.63 (1H, dd, H5, $J_{5,4}$ 7.6, J_{gem} 11.7), 3.75 (1H, dd, H5′, $J_{5',4}$ 5.6, J_{gem} 11.7), 4.13 (1H, a-t, H3, J 4.4), 4.24 (1H, dt, H2, $J_{2,3}$ 4.4, J 7.3); δ_C (D_2O, 100.6 MHz): 48.1 (C1), 59.4 (C5), 61.8 (C4), 71.0 (C2), 71.4 (C3); LRMS (ESI+ve): m/z (%) 134 (100) $[M+H]^+$.

For the enantiomer **1D**, 75%, mp 151–154 °C, $[\alpha]_D^{20} = +18.2$ (c 0.85, H_2O) (lit.[17e] mp 159–161 °C, $[\alpha]_D^{20} = +19.8$ (c 0.45, H_2O); lit.[5] mp 157–159 °C, $[\alpha]_D^{20} = +18.8$ (c 0.16, H_2O)).

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