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## Enantiomeric 2-acetamido-1,4-dideoxy-1,4-iminoribitols as potential pyrrolidine hexosaminidase inhibitors

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## ABSTRACT

2-Acetamido-1,4-imino-1,2,4-trideoxy-D-ribitol (DRBNAC) and the enantiomeric LRBNAc were prepared as potential hexosaminidase inhibitors from L- and D-lyxonolactone, respectively. Neither *N*-benzyl-DRBNAC nor *N*-benzyl-LRBNAc showed any inhibition of  $\alpha$ - or  $\beta$ -hexosaminidases or any other glycosidase.

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### 1. Introduction

Deficiencies of  $\alpha$ - and  $\beta$ -hexosaminidases are responsible for a number of lysosomal storage diseases; lack of enzymes to cleave a terminal *N*-acetyl- $\beta$ -D-glucosamine unit gives rise to Sanfilippo [1], Tay-Sachs and Sandhoff [2] diseases whereas lack of an enzyme to hydrolyze a terminal *N*-acetyl- $\alpha$ -D-galactosamine component is associated with Schindler-Kanzaki disease [3]. Inhibition of hexosaminidases may also provide strategies for the treatment of osteoarthritis [4], cancer [5], and type II diabetes [6]; thus the design of specific and potent hexosaminidase inhibitors provides an attractive synthetic target.

Iminosugars – in which the ring oxygen of the carbohydrate is replaced by nitrogen – constitute a family of both natural and synthetic inhibitors of glycosidases [7]. DNJNAC **1** [8], the corresponding analogue of *N*-acetyl- $\alpha$ -D-glucosamine, and its *N*-alkyl analogues [9] – as well as

other synthetic piperidine pyranose mimics [10] – are potent inhibitors of  $\beta$ -hexosaminidases (Fig. 1). The natural product nagstatin **2** [11], with a *galacto*-configuration in the piperidine ring, is also a potent inhibitor of  $\beta$ -hexosaminidases [12]. The analogue of *N*-acetyl- $\alpha$ -D-galactosamine **3** is the only powerful inhibitor of *N*-acetyl- $\alpha$ -D-galactosaminidases (GalNAcases) yet reported [13]. Hydroxyazepane [14] mimics of *N*-acetyl-hexosamines, such as the azepanes **4** and **5**, are specific sub-micromolar inhibitors of  $\beta$ -hexosaminidases [15]. Pochonicine **6** [or its enantiomer], a nanomolar pyrrolizidine  $\beta$ -hexosaminidase inhibitor, has been isolated from *Pochonia suchlasporia* var. *suchlasporia* TAMA 87 [16].

Pyrrolidine analogues of pentoses provide examples of powerful glycosidase inhibitors. The natural product DAB **7D**, isolated from *Arachniodes standishii* and *Angylocalyx boutiqueanus* [17], shows strong inhibition of  $\alpha$ -glucosidases and weaker inhibition of several other glycosidases; the unnatural enantiomer LAB **7L** is also a potent – but highly specific – inhibitor of  $\alpha$ -glucosidases [18] (Scheme 1). A significant number of L-enantiomers of imino-D-sugar mimics show inhibition of the *same* glycosidases [19]. Both DABNAC **8D** and LABNAC **8L**, the NAc analogues of DAB **7D** and LAB **7L** were synthesised from the

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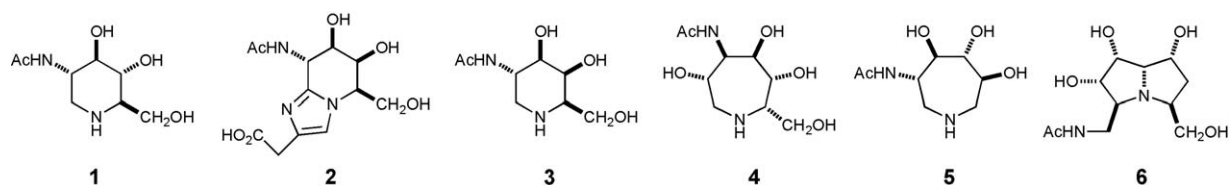


Fig. 1. Potent inhibitors of hexosaminidases.

enantiomers of lyxonolactone [20]. LABNAc **8L** and its *N*-alkyl analogues [such as the *N*-benzyl derivative] were micromolar – whereas DABNAc **8D** analogues were weak – specific inhibitors of  $\beta$ -hexosaminidases; neither showed any inhibition of  $\alpha$ -GalNAcases [21].

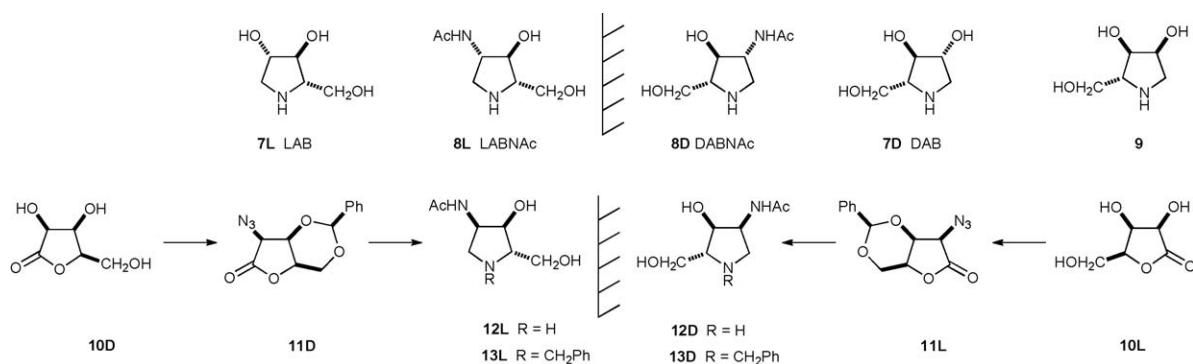
The imino ribitol **9**, isolated from the mulberry tree *Morus alba* [22] and synthesized from carbohydrate [23] and non-carbohydrate [24] starting materials, was a weak inhibitor of several glycosidases ( $IC_{50}$  = 230–610  $\mu$ M) [13], but was shown to mimic a galactose motif by its moderate inhibition of a  $\beta$ -D-galactosidase (rat intestinal lactase,  $IC_{50}$  17  $\mu$ M) [25]. LRBNAc **12L** and DRBNAc **12D** are related to **9** in the same way that LABNAc **8L** and DABNAc **8D** are related to LAB **7L** and DAB **7D**. Accordingly, in the search for GalNAcase inhibitors, the syntheses of LRBNAc **12L** from D-lyxonolactone **10D** and of DRBNAc **12D** from L-lyxonolactone **10L** (Scheme 1) – which depend on the efficient introduction of an azide at C2 with *retention* of configuration in suitably protected intermediates **11L** and **11D** – are herein described. However, this paper reports that neither DRBNAc **12D** nor LRBNAc **12L** showed significant inhibition of any glycosidase.

The key steps in the synthesis of LABNAc **8L** from D-lyxonolactone **10D** were introduction of nitrogen by nucleophilic substitution with inversion at C2, and formation of the pyrrolidine ring by nucleophilic substitutions by benzylamine between C5 and C2 [with inversion of configuration] of the D-lyxo sugar to give the required *L-ribo* configuration. Reaction of D-lyxonolactone **10D** with benzaldehyde and hydrochloric acid gave the highly crystalline benzylidene derivative **14D** (90% yield) in which only the C2-OH group of the lactone is unprotected (Scheme 2).

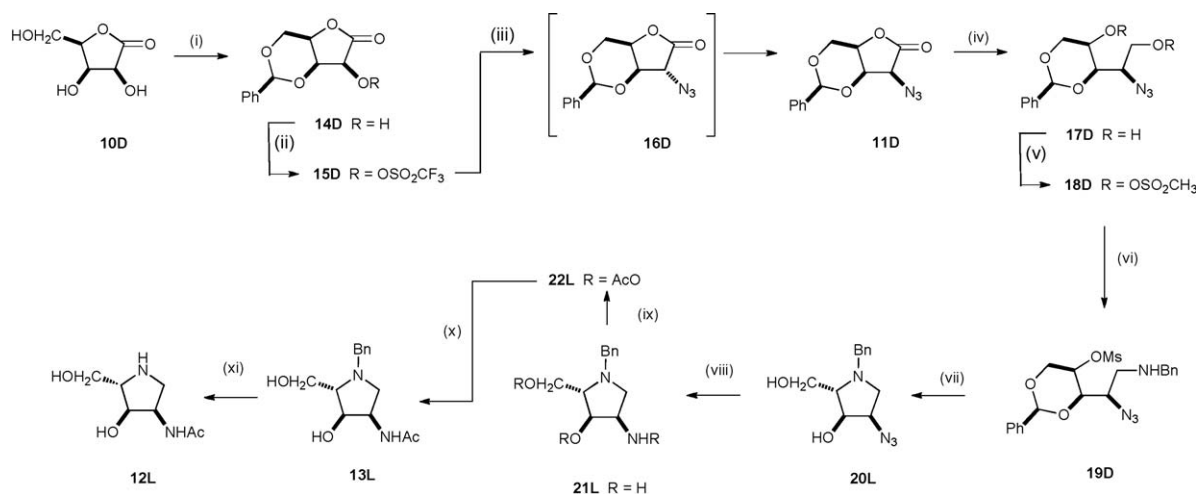
There are two strategies for the introduction of azide at C2 of **10D** with retention of configuration. One route

involves two successive  $S_N2$  reactions; initial inversion by trifluoroacetate displacement of a triflate to afford the epimeric alcohol [26], with a subsequent  $S_N2$  displacement of the epimeric triflate by azide to give overall retention of configuration [27]. An alternative approach depends on the observation that, in general, azides which are *cis* to all the other substituents on a lactone ring are thermodynamically more stable than epimers in which the azide is the sole *trans* substituent [28]; there are even examples where base catalysed epimerization of the less stable kinetic triflate is so rapid that it is not possible to isolate the kinetic azide but only the thermodynamic azide with retention of configuration [29]. Esterification of **14D** with triflic (trifluoromethanesulfonic) anhydride in pyridine gave the corresponding triflate **15D** in quantitative yield [extra care must be taken in the handling of this triflate, as a co-worker experienced a strong allergic response to this compound or its decomposition products]. Treatment of the *lyxono*-triflate **15D** with sodium azide in DMF produced 83% yield of the *xylono*-azide **16D** under kinetic control using a short reaction time (50–60 min) and just under stoichiometric amounts of sodium azide (0.97 equivalents) during the reaction [21,28]. However, when the triflate **15D** was left for 20 h at room temperature in the presence of excess sodium azide and pyridinium *p*-toluenesulfonate (PPTS) the thermodynamic *lyxono*-azide **11D** was formed in 86% yield with a trace of the easily separable *xylono*-azide **16D** (4%).

The sensitivity of  $\alpha$ -azidolactones to base frequently results in low yields of direct conversion of the lactone to the corresponding diol by hydrides [27]. Attempted reductions of the azidolactone **11D** with lithium borohydride, sodium borohydride or Super-Hydride<sup>®</sup> gave low yields of the *lyxo*-diol **17D**. However, L-Selectride<sup>®</sup> in THF at  $-30$  °C gave acceptable yields for the formation of *lyxo*-



Scheme 1. Relationships between pyrrolidine glycosidase inhibitors.



**Scheme 2.** Reagents and conditions: (i) PhCHO, HCl, 90% (ii) Tf<sub>2</sub>O, pyridine, -50 °C, 2.5 h, 100%; (iii) NaN<sub>3</sub>, PPTS, DMF, RT, 20 h, 86% **11D**, 4% **16D**; (iv) L-Selectride<sup>®</sup>, THF, -78 °C, 2 h, 57%; (v) MsCl, Et<sub>3</sub>N, DCM, 0 °C, 2 h, 92%; (vi) BnNH<sub>2</sub>, 95 °C, 20 h, 80%; (vii) Amberlyst<sup>®</sup> 15 beads, 1,4-dioxane, H<sub>2</sub>O, 95 °C, 14 h; (viii) PPh<sub>3</sub>, H<sub>2</sub>O, THF, RT, 14 h, 89%; (ix) Ac<sub>2</sub>O, pyridine, RT, 14 h, 85%, (x) NaOMe, MeOH, RT, 2 h, 91%; (xi) H<sub>2</sub>/Pd black, 1,4-dioxane, H<sub>2</sub>O, r.t., 18 h, 88%.

diol **17D** (57%); after the reduction was complete, it was necessary to employ an oxidative workup procedure using sodium hydroxide and aqueous hydrogen peroxide to remove the borane adducts in order to obtain a reasonable yield of pure material after flash chromatography. Esterification of the *lyxo*-diol **17D** with mesyl (methanesulfonyl) chloride in dichloromethane in the presence of triethylamine at 0 °C afforded the dimesylate **18D** in 90% yield. Reaction of the dimesylate **18D** with benzylamine at 95 °C for 20 h gave the aminobenzylmesylate **19D** in 80% yield; there was no subsequent intramolecular cyclization since the resulting pyrrolidine would have a benzylidene acetal *trans* to the pyrrolidine ring. Deprotection of the benzylidene acetal of **19D** which would allow subsequent cyclization to the pyrrolidine **20L**, was achieved by heating **19D**, in aqueous dioxane in the presence of acid ion-exchange resin at 95 °C for 14 h. After filtering off the resin, washing with 2 M ammonium hydroxide solution, solvent removal and flash chromatography, the *L*-ribo-pyrrolidine **20L** was isolated in 89% yield. Staudinger reduction [30] of the azide **20L** by triphenylphosphine and water in THF gave, after purification by ion-exchange chromatography, the *L*-ribo-amine **21L** in 89% yield. Reaction of the aminodiol **21L** with acetic anhydride in pyridine afforded the triacetyl derivative **22L** (85% yield). The *O*-acetyl groups in **22L** were selectively removed by treatment with catalytic sodium methoxide in methanol to give *N*-benzyl-L-ribonolactone **13L**, in 91% yield; the structure of **13L** was unequivocally established by X-ray crystallographic analysis [31]. Removal of the *N*-benzyl group in **13L** by hydrogenolysis in the presence of palladium black in aqueous 1,4-dioxane gave L-ribonolactone **12L** in 88% yield. The preparation of L-ribonolactone **12L** from D-lyxonolactone was achieved in 18% overall yield over the 12 steps.

DRBNac **12D** was prepared from 3,5-benzylidene-*L*-lyxonolactone **10L** by an identical procedure; the benzylidene lactone **10L** was formed in 95% yield [21] from 2,3-isopropylidene-*L*-lyxonolactone, readily available on a large scale from D-ribose [32].

## 2. Inhibition studies

Neither *N*-benzyl-DRBNac **13D** nor *N*-benzyl-L-ribonolactone **13L** showed significant inhibition of the hydrolysis of the corresponding *p*-nitrophenyl glycosides by any of the following range of enzymes: α-glucosidase (yeast), β-glucosidase (almond), α-galactosidase (coffee bean), β-galactosidase (jack bean), α-mannosidase (jack bean), β-mannosidase (snail), α-fucosidase (bovine), β-xylosidase (*Aspergillus niger*), β-*N*-acetylhexosaminidase (jack bean), and α-*N*-acetylgalactosaminidase (*Charonia lampas*). In particular, there was no inhibition of any α- or β-hexosaminidases.

## 3. Summary

The synthesis of L-ribonolactone **12L** from D-lyxonolactone **10D** over 12 steps proceeded in a good overall yield of 18%. The enantiomer DRBNac **12D** was also prepared from *L*-lyxonolactone. Assays of *N*-benzyl-L-ribonolactone **13L** and *N*-benzyl-DRBNac **13L** showed there was no significant inhibition of either β-*N*-acetylhexosaminidase (jack bean) or α-*N*-acetylgalactosaminidase (*Charonia lampas*).

## 4. Experimental

THF was distilled from sodium benzophenone ketyl or purchased dry from Aldrich in Sure/Seal<sup>™</sup> bottles and recapped with Oxford Sure/Seal<sup>™</sup> valve-caps. *N,N*-Dimethylformamide (DMF) and pyridine were purchased dry from Aldrich in Sure/Seal<sup>™</sup> bottles and were recapped with Oxford Sure/Seal<sup>™</sup> valve caps. Water was distilled. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed under an atmosphere of nitrogen, argon, or hydrogen gas were maintained by an inflated balloon. Imidazole was recrystallised from dichloromethane. All other reagents were used as supplied without prior purification. Thin-layer chromatography (TLC) was per-

formed on aluminium-backed sheets coated with 60 F<sub>254</sub> silica. Sheets were developed by dipping in a solution of cerium(IV) sulfate (0.2% w/v) and ammonium molybdate (5%) in 2 M sulfuric acid and heating with a heat gun. Flash column chromatography was performed using Sorbosil<sup>®</sup> C<sub>60</sub> 40/60 silica. Ion-exchange chromatography was performed using either Amberlite<sup>®</sup> CG-150 or Dowex<sup>®</sup> 50WX8–200, as stated. NMR spectra were recorded on a Bruker DQX 400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C: 100 MHz) spectrometer at room temperature in the deuterated solvent stated. All chemical shifts ( $\delta$ ) are quoted in ppm. Coupling constants (<sup>3</sup>J) are quoted in Hz. Residual signals from the solvents were used as an internal reference. The <sup>13</sup>C resonances were assigned using either DEPT or APT sequences or from <sup>1</sup>H–<sup>13</sup>C HMQC and HMBC spectra. Melting points were recorded on a Kofler hot block and are uncorrected. IR spectra were recorded at room temperature on a PerkinElmer 1750 IR Fourier transform spectrophotometer or a Bruker Tensor 27 FTIR spectrometer, using thin films on NaCl or Ge plates, as stated, and were recorded over 16 or 32 scans at a resolution of 4 cm<sup>-1</sup>. Only the characteristic peaks are quoted. Mass spectrometry: high-resolution mass spectra (HRMS) were recorded on a micromass Autospec 500 OAT spectrometer using the technique of chemical ionisation (CI), or on a Waters 2790-Micromass LCT mass spectrometer using the technique of electrospray ionisation (ESI). Optical rotations were recorded on a PerkinElmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g(100 mL)<sup>-1</sup>. The wavelength at which the rotations were measured corresponds to the sodium D line (ca. 589 nm). Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

## 5. Enzyme inhibition assays

All enzymes and corresponding PNP substrates were obtained from Sigma, apart from coffee bean  $\alpha$ -D-galactosidase, jack bean  $\beta$ -D-galactosidase,  $\alpha$ -D-mannosidase and  $\beta$ -N-acetyl-D-hexosaminidase, and *Charonia lampas*  $\alpha$ -N-acetyl-D-galactosaminidase, which were purified from the natural sources in the Oxford Glycobiology Institute. *Enzyme solutions*: For the purposes of this investigation, all enzyme solutions were made up using 50 mM citrate–phosphate buffer (anhydrous disodium hydrogen phosphate dissolved in citric acid) at pH 5 containing 1 mg mL<sup>-1</sup> bovine serum albumin (BSA) and 0.02% NaN<sub>3</sub>, except  $\alpha$ -D-glucosidase, for which Dulbecco's phosphate buffered saline (PBS) buffer at pH 7.4 was used. These solutions were stored on ice whilst in use and at –20 °C when not in use. *Inhibitor solutions*: NBn-LRBNac **13L** and NBn-DRBNac **13D** were dissolved in distilled water at a concentration of 10 mg mL<sup>-1</sup>. These solutions were stored on ice whilst in use and at –20 °C when not in use. *Enzyme substrate solutions*: Substrate solutions were made from a stock solution (3 mM) in 10 mL batches, as required, by dissolving the appropriate mass of substrate in the appropriate buffer solution for the enzyme. These were kept at 4 °C when not in use. *Method*: Assays were carried out in triplicate, using H<sub>2</sub>O as a blank in place of the

inhibitor. The concentrations of the enzyme were adjusted so that the reading for the final absorbance was in the range of 0.5–1.5 units over a reaction time of 20 min. For example,  $\beta$ -N-acetyl-D-hexosaminidase was diluted from 6 U mL<sup>-1</sup> to 0.4 U mL<sup>-1</sup> by experiment. Linearity over the time course of the reaction was checked using a series of incubation times. The following were combined in the well of a flat-bottomed 96-well (300 mL) microtitre plate: 5  $\mu$ L enzyme solution, 5  $\mu$ L inhibitor solution, and 40  $\mu$ L substrate solution. The reaction mix was incubated at 37 °C for 20 min (Denley Wellwarm 1) and was quenched by the addition of 200  $\mu$ L of 0.5 M Na<sub>2</sub>CO<sub>3</sub>. Absorbance at 405 nm was measured immediately using a microtitre plate reader (Molecular Devices UVmax kinetic microplate reader and SOFTmax 2.35 software).

## 6. 2-Azido-3,5-O-benzylidene-2-deoxy-D-lyxono-1,4-lactone **11D**

Triflic anhydride (2.44 mL, 14.5 mmol, 1.6 equivalents) was added dropwise to a stirred solution of the benzylidene lactone **14D**<sup>21</sup> (2.14 g, 9.06 mmol) in pyridine (20 mL) at –50 °C under an atmosphere of nitrogen. The temperature was allowed to rise to room temperature during the course of the reaction. After 2.5 h, analysis by TLC (ethyl acetate) showed no residual starting material (*R*<sub>f</sub> 0.07) and a major spot due to the product (*R*<sub>f</sub> 0.50). The solvents were removed *in vacuo*, by coevaporation with toluene (high vacuum). The residue was partitioned between ethyl acetate (80 mL) and 0.1 M HCl (50 mL). The resulting biphasic solution was separated and the organic layer washed with brine (50 mL). The aqueous phase was extracted with ethyl acetate (3  $\times$  15 mL) and the combined organic phase was dried (magnesium sulfate) and the solvents removed *in vacuo*. Sodium azide (1.46 g, 22.6 mmol, 2.5 equivalents) was added to a stirred solution of crude triflate **15D** (ca. 3.34 g, 9.06 mmol) in DMF (35 mL) at room temperature under an atmosphere of nitrogen. After 1 h, PPTS (2.73 g, 10.9 mmol) was added. After a further 18 h, analysis by TLC (1:1, ethyl acetate/cyclohexane) showed a major product spot (*R*<sub>f</sub> 0.17) and a minor spot (*R*<sub>f</sub> 0.41). The solvents were removed *in vacuo*, by coevaporation with toluene (high vacuum); the residue was purified by flash chromatography (3:1  $\rightarrow$  1:1, cyclohexane/ethyl acetate) to give the azido-lyxono-lactone **11D** (2.04 g, 7.81 mmol, 86%) as a white solid, m.p. 122–123 °C, 128–130 °C (recrystallised from ethyl acetate/cyclohexane) [Lit. [28] 121–122 °C (acetone)]; [ $\alpha$ ]<sub>D</sub><sup>23</sup> +37.5 (c 0.99, acetone) [Lit. [28] [ $\alpha$ ]<sub>D</sub><sup>24</sup> +37.4 (c 1.00, acetone)];  $\nu$ <sub>max</sub> (NaCl) 2119 (N<sub>3</sub>), 1796 (C=O) cm<sup>-1</sup>;  $\delta$ <sub>H</sub>(400 MHz; (CD<sub>3</sub>)<sub>2</sub>CO) 4.40 (1H, dd, *J*<sub>5,5'</sub> 13.8 Hz, *J*<sub>5,4</sub> 2.0 Hz, H-5), 4.49 (1H, dd, *J*<sub>5,5'</sub> 13.8 Hz, *J*<sub>5,4</sub> 1.3 Hz, H-5'), 4.60 (1H, d, *J*<sub>2,3</sub> 4.1 Hz, H-2), 4.65 (1H, dt, *J*<sub>4,5'</sub> 1.3 Hz, *J*<sub>4,5</sub> 2.0 Hz, *J*<sub>4,3</sub> 2.0 Hz, H-4), 5.13 (1H, dd, *J*<sub>3,4</sub> 2.0 Hz, *J*<sub>3,2</sub> 4.1 Hz, H-3), 5.80 (1H, s, CHPh), 7.36–7.52 (5H, m, CH(Ar)).  $\delta$ <sub>C</sub>(100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 62.4 (C-2), 66.5 (C-5), 71.9 (C-4), 75.3 (C-3), 99.1 (CHPh), 126.5, 128.5, 129.4 (CH(Ar)), 138.1 (C(Ar)), 171.7 (C=O) ppm; Found: C, 55.13; H, 4.33; N, 16.08; C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub> requires C, 55.17; H, 4.24; N, 16.09%; a small amount of azido-xylono-lactone **16D**<sup>21</sup> (97.2 mg, 0.372 mmol, 4%) was also isolated.

The enantiomeric azidolactone **11L**, m.p. 128–130 °C;  $[\alpha]_D^{25} -41.3$  (c 0.99, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **11D**.

## 7. 2-Azido-3,5-O-benzylidene-2-deoxy-D-lyxitol **17D**

A 1 M solution of L-Selectride® in THF (2.87 mL, 2.5 equivalents) was added dropwise to a stirred solution of the *lyxono*-lactone **11D** (300 mg, 1.15 mmol) in THF (3.0 mL) at –78 °C under an atmosphere of argon in the presence of molecular sieve (4 Å). After 2 h, analysis by TLC (ethyl acetate) showed a major spot due to the product ( $R_f$  0.50) and no residual starting material ( $R_f$  0.59). Methanol (0.5 mL) was added slowly to destroy the excess hydride and after 15 min a further portion (2.5 mL) was added. After a further 2 h, the mixture was filtered over Celite®; diethyl ether (10 mL) and a 50% *v/v* solution of 4 M NaOH/35% aqueous H<sub>2</sub>O<sub>2</sub> (5 mL) were added to the filtrate and the reaction mixture allowed to stir for 1 h. The resulting biphasic solution was separated and the aqueous phase was extracted using ethyl acetate (3 × 2 mL). The combined organic phase was dried (magnesium sulfate) and the solvents were removed *in vacuo*. The residue was passed through a silica plug (9:1 ethyl acetate/methanol) to yield the diol **17D** (175 mg, 57%) as a white amorphous solid, m.p. 102–103 °C;  $[\alpha]_D^{23} -42.6$  (c 0.345, CHCl<sub>3</sub>);  $\nu_{\max}$  (NaCl) 3417 (OH), 2103 (N<sub>3</sub>) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, CDCl<sub>3</sub>) 2.14 (1H, br s, OH), 2.77 (1H, br s, OH), 3.77 (1H, apparent q,  $J$  1.5 Hz, H-4), 3.81 (1H, dd,  $J_{1,1'}$  11.4 Hz,  $J_{1,2}$  4.8 Hz, H-1), 3.84–3.89 (1H, m, H-2), 3.91 (1H, dd,  $J_{3,2}$  9.2 Hz,  $J_{3,4}$  1.2 Hz, H-3), 3.98 (1H, dd,  $J_{1,1'}$  11.4 Hz,  $J_{1,2}$  3.0 Hz, H-1'), 4.10 (1H, dd,  $J_{5,5'}$  12.1 Hz,  $J_{5,4}$  1.4 Hz, H-5), 4.29 (1H, dd,  $J_{5,5'}$  12.1 Hz,  $J_{5,4}$  2.0 Hz, H-5'), 5.57 (1H, s, CHPh), 7.35–7.48 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, CDCl<sub>3</sub>) 62.0 (C-1), 62.1 (C-2), 63.3 (C-4), 72.4 (C-5), 78.0 (C-3), 101.4 (CHPh), 125.8, 128.4, 129.3 (CH(Ar)), 137.2 (C(Ar));  $m/z$  HRMS (ESI<sup>-</sup>): Found 264.0985, C<sub>12</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub> [M-H]<sup>-</sup> requires 264.0984.

The enantiomeric diol **17L**, m.p. 101–102 °C;  $[\alpha]_D^{23} +43.8$  (c 0.85, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **17D**.

## 8. 2-Azido-3,5-O-benzylidene-2-deoxy-1,4-di-O-methanesulfonyl-D-lyxitol **18D**

Triethylamine (0.60 mL, 4.32 mmol, 4 equiv.) was added to a stirred solution of the diol **17D** (287 mg, 1.08 mmol) in dichloromethane (6.0 mL) at 0 °C under an atmosphere of nitrogen. After 20 min, methanesulfonyl chloride (0.34 mL, 4.32 mmol, 4 equiv.) was added dropwise. After 2 h, analysis by TLC (ethyl acetate) showed no residual starting material ( $R_f$  0.56) and a major spot due to the product ( $R_f$  0.67) [Note: change in the colour of the spot made it easier to see the progress of the reaction]. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (20 mL) and brine (30 mL). The layers were separated and the aqueous phase was extracted using ethyl acetate (3 × 10 mL). The combined organic phase was dried (magnesium sulfate), the solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography (1:1,

cyclohexane/ethyl acetate) to afford the dimesylate **18D** (421 mg, 92%) as a white crystalline solid, m.p. 139–140 °C;  $[\alpha]_D^{20} -75.5$  (c 0.97, CHCl<sub>3</sub>);  $\nu_{\max}$  (NaCl) 2108 (N<sub>3</sub>), 1346 and 1180 (S=O) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, CDCl<sub>3</sub>) 3.08, 3.20 (6H, 2 × s, 2 × SO<sub>2</sub>CH<sub>3</sub>), 3.94 (1H, dd,  $J_{3,2}$  9.7 Hz,  $J_{3,4}$  1.6 Hz, H-3), 4.06 (1H, ddd,  $J_{2,3}$  9.7 Hz,  $J_{2,1}$  5.9 Hz,  $J_{2,1'}$  2.6 Hz, H-2), 4.14 (1H, dd,  $J_{5,5'}$  13.4 Hz,  $J_{5,4}$  1.2 Hz, H-5), 4.50 (1H, dd,  $J_{1,1'}$  10.9 Hz,  $J_{1,2}$  5.9 Hz, H-1), 4.58 (1H, dd,  $J_{5,5'}$  13.4 Hz,  $J_{5,4}$  1.8 Hz, H-5'), 4.61 (1H, dd,  $J_{1,1'}$  10.9 Hz,  $J_{1,2}$  2.6 Hz, H-1'), 4.87–4.90 (1H, m, H-4), 5.57 (1H, s, CHPh), 7.37–7.50 (5H, m, CH(Ar));  $\delta_C$  (100 MHz, CDCl<sub>3</sub>): 37.7, 39.2 (2 × SO<sub>2</sub>CH<sub>3</sub>), 58.7 (C-2), 67.8 (C-1), 69.4 (C-5), 70.0 (C-4), 75.4 (C-3), 101.3 (CHPh), 126.0, 128.4, 129.5 (CH(Ar)), 136.5 (C(Ar));  $m/z$  HRMS (ESI<sup>+</sup>): Found 444.0511, C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>8</sub>Na [M+Na]<sup>+</sup> requires 444.0511. Found: C, 39.81; H, 4.78; N, 9.95; C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>8</sub>S<sub>2</sub> requires C, 39.90; H, 4.54; N, 9.97%.

The enantiomeric dimesylate **18L**, m.p. 138–140 °C;  $[\alpha]_D^{23} +78.5$  (c 0.96, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **18D**.

## 9. 1-Aminobenzyl-2-azido-3,5-O-benzylidene-1,2-dideoxy-4-O-methanesulfonyl-D-lyxitol **19D**

The dimesylate **18D** (669 mg, 1.59 mmol) was dissolved in benzylamine (14.0 mL) and the resulting solution heated at 95 °C. After 20 h, analysis by TLC (1:1, cyclohexane/ethyl acetate) showed one major spot ( $R_f$  0.32) and a UV active spot ( $R_f$  0.59) due to residual benzylamine. The solvents were removed *in vacuo* by co-evaporation with toluene. The resulting orange residue was partitioned between ethyl acetate (30 mL) and brine (40 mL). The layers were separated and the aqueous phase was extracted using ethyl acetate (3 × 15 mL). The combined organic phase was dried (magnesium sulfate), the solvents were removed *in vacuo* and the resulting residue was purified by flash chromatography (9:1 → 1:1, cyclohexane/ethyl acetate) to yield the aminomesylate **19D** (551 mg, 1.27 mmol, 80%) as a white amorphous solid, m.p. 89–91 °C;  $[\alpha]_D^{20} -45.6$  (c 0.97, CHCl<sub>3</sub>);  $\nu_{\max}$  (NaCl) 3355 (N-H), 2106 (N<sub>3</sub>), 1354 and 1175 (S=O) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, CDCl<sub>3</sub>) 2.00 (1H, br s, NHBn), 2.95 (1H, dd,  $J_{1,1'}$  13.0 Hz,  $J_{1,2}$  6.1 Hz, H-1), 3.16 (1H, dd,  $J_{1,1'}$  13.0 Hz,  $J_{1,2}$  3.3 Hz, H-1'), 3.17 (3H, s, SO<sub>2</sub>CH<sub>3</sub>), 3.82 (1H, d,  $J$  13.3 Hz, NCHH'Ph), 3.87 (1H, ddd,  $J_{2,3}$  9.7 Hz,  $J_{2,1}$  6.1 Hz,  $J_{2,1'}$  3.3 Hz, H-2), 3.93 (1H, d,  $J$  13.3 Hz, NCHH'Ph), 4.02 (1H, dd,  $J_{3,2}$  9.7 Hz,  $J_{3,4}$  1.1 Hz, H-3), 4.12 (1H, dd,  $J_{5,5'}$  13.4 Hz,  $J_{5,4}$  1.0 Hz, H-5), 4.61 (1H, dd,  $J_{5,5'}$  13.4 Hz,  $J_{5,4}$  1.6 Hz, H-5'), 4.87 (1H, apparent d,  $J$  1.3 Hz, H-4), 5.57 (1H, s, CHPh), 7.22–7.45 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, CDCl<sub>3</sub>) 39.42 (SO<sub>2</sub>CH<sub>3</sub>), 48.7 (C-1), 53.8 (NCH<sub>2</sub>Ph), 60.3 (C-2), 69.6 (C-5), 71.0 (C-4), 76.7 (C-3), 101.2 (CHPh), 126.0, 127.2, 128.1, 128.3, 128.5, 129.3 (CH(Ar)), 136.9, 139.5 (C(Ar));  $m/z$  HRMS (ESI<sup>+</sup>): found 433.1547, C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub>S [M+H]<sup>+</sup> requires 433.1546. Found: C, 55.57; H, 5.69; N, 12.56; C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>S requires C, 55.54; H, 5.59; N, 12.95%.

The enantiomeric aminomesylate **19L**, m.p. 91–92 °C;  $[\alpha]_D^{22} +40.5$  (c 1.0, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **19D**.

## 10. *N*-Benzyl-2-azido-1,4-imino-1,2,4-trideoxy-*L*-ribitol **20L**

Amberlyst<sup>®</sup> 15 (wet) beads were added to a stirred solution of the aminomesylate **19D** (540 mg, 1.25 mmol) in 1,4-dioxane (20 mL) and water (20 mL) and the resulting mixture was heated at 95 °C under an atmosphere of nitrogen. After 14 h, analysis by TLC (ethyl acetate) showed one spot ( $R_f$  0.23) due to the product. After cooling to room temperature, 2 M NH<sub>4</sub>OH (aq) solution (10 mL) was added and the mixture was stirred for 2 h. The beads were filtered off, washing thoroughly with 2 M NH<sub>4</sub>OH (3 × 5 mL) and 1,4-dioxane (10 mL). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (ethyl acetate) to give the imino-*L*-ribitol **20L** (275 mg, 89%) as a pale brown oil;  $[\alpha]_D^{20} +23.9$  (c 0.92, CHCl<sub>3</sub>);  $\nu_{\max}$  (NaCl) 3384 (OH), 2106 (N<sub>3</sub>) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, CDCl<sub>3</sub>) 2.69 (1H, dd,  $J_{1,1'}$  9.9 Hz,  $J_{1,2}$  7.3 Hz, H-1), 2.77 (1H, br s, OH), 2.85 (1H, m, H-4), 3.26 (1H, dd,  $J_{1',1}$  9.9 Hz,  $J_{1',2}$  6.1 Hz, H-1'), 3.57–3.67 (3H, m, NCHH'Ph, H-5, H-5'), 3.91 (1H, dt,  $J_{2,1}$  7.3 Hz,  $J$  5.7 Hz, H-2), 3.97 (1H, d,  $J$  13.0 Hz, NCHH'Ph), 4.24 (1H, apparent t,  $J$  4.9 Hz, H-3) 7.26–7.38 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, CDCl<sub>3</sub>) 55.0 (C-1), 58.9 (NCH<sub>2</sub>Ph), 60.0 (C-5), 61.9 (C-2), 70.8 (C-4), 74.1 (C-3), 127.7, 128.6, 128.8 (CH(Ar)), 137.6 (C(Ar));  $m/z$  HRMS (ESI<sup>+</sup>): Found 249.1344, C<sub>12</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> requires 249.1352.

The enantiomeric benzylamine **20D**, oil;  $[\alpha]_D^{23} -31.5$  (c 0.955, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **20L**.

## 11. 2-Amino-*N*-benzyl-1,4-imino-1,2,4-trideoxy-*L*-ribitol **21L**

Triphenyl phosphine (169 mg, 0.644 mmol) was added to a stirred solution of the azide **20L** (80.0 mg, 0.322 mmol) and water (12 μL, 0.322 mmol) in THF (1.0 mL) at room temperature under an atmosphere of nitrogen. After 14 h, analysis by TLC (ethyl acetate) showed a major product spot (baseline) and no residual starting material ( $R_f$  0.23). The solvents were removed *in vacuo* and the remaining residue was partitioned between chloroform (3 mL) and water (2 mL). The aqueous layer was extracted with chloroform (3 × 1 mL) to remove excess triphenylphosphine oxide. The organic layer was extracted with water (3 × 1 mL); the combined aqueous phase was purified by ion exchange chromatography (Dowex<sup>®</sup> 50WX8-200) to afford the amine **21L** (64.0 mg, 0.288 mmol, 89%) as a colourless oil;  $[\alpha]_D^{22} +63.9$  (c 0.98, H<sub>2</sub>O);  $\nu_{\max}$  (Ge) 3356 (OH, NH<sub>2</sub>), 1585 (NH<sub>2</sub>) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, D<sub>2</sub>O) 2.38 (1H, apparent t,  $J$  10.1 Hz, H-1), 2.72 (1H, dt,  $J_{4,3}$  2.6 Hz,  $J_{4,5}$  5.9 Hz,  $J_{4,5'}$  5.9 Hz, H-4), 2.96 (1H, dd,  $J_{1,1'}$  9.3 Hz,  $J_{1',2}$  6.5 Hz, H-1'), 3.19 (1H, ddd,  $J_{2,1}$  10.9 Hz,  $J_{2,1'}$  6.5 Hz,  $J_{2,3}$  5.6 Hz, H-2), 3.40 (2H, d,  $J_{5/5',4}$  5.9 Hz, H-5, H-5'), 3.59 (1H, d,  $J$  12.3 Hz, NCHHPh), 3.85 (1H, d,  $J$  12.3 Hz, NCHHPh), 3.94 (1H, dd,  $J_{3,2}$  5.6 Hz,  $J_{3,4}$  2.6 Hz, H-3), 7.30–7.41 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, D<sub>2</sub>O): 51.3 (C-2), 57.0 (C-1), 59.5 (NCH<sub>2</sub>Ph), 61.7 (C-5), 72.6 (C-4), 73.4 (C-3), 128.2, 128.9, 130.4 (CH(Ar)), 137.1 (C(Ar));  $m/z$  HRMS (ESI<sup>+</sup>): Found 223.1448, C<sub>12</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> requires 223.1447.

The enantiomeric diamine **21D**, oil;  $[\alpha]_D^{23} -64.2$  (c 0.965, H<sub>2</sub>O), was prepared by a similar method. All other physical data was identical to that of **21L**.

## 12. 2-Acetamido-*N*-benzyl-3,5-di-*O*-acetyl-1,4-imino-1,2,4-trideoxy-*L*-ribitol **22L**

Acetic anhydride (0.15 mL, 1.620 mmol) was added dropwise to a stirred solution of the amine **21L** (60.0 mg, 0.270 mmol) in pyridine (2.0 mL) at room temperature under an atmosphere of argon. After 14 h, analysis by TLC (ethyl acetate) showed no residual starting material (baseline) and a spot due to the product ( $R_f$  0.21). The solvents were removed *in vacuo* using toluene to aid by coevaporation; the remaining residue was purified by flash chromatography (98:2, ethyl acetate/triethylamine) to form the triacetate **22L** as a colourless oil (79.8 mg, 0.229 mmol, 85%);  $[\alpha]_D^{22} +79.2$  (c 0.98, CHCl<sub>3</sub>);  $\nu_{\max}$  (NaCl) 3286 (N-H), 1742 (C=O ester), 1654 (C=O amide band I), 1542 (N-H amide band II) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, C<sub>6</sub>D<sub>6</sub>) 1.65 (3H, s, amide CH<sub>3</sub>), 1.72 (3H, s, C(O)CH<sub>3</sub>), 1.89 (3H, s, C(O)CH<sub>3</sub>), 2.27 (1H, dd,  $J_{1,1'}$  8.1 Hz,  $J_{1,2}$  10.7 Hz, H-1), 2.94 (1H, ddd,  $J_{4,5'}$  5.9 Hz,  $J_{4,5}$  4.3 Hz,  $J_{4,3}$  1.5 Hz, H-4), 3.15 (1H, dd,  $J_{1',1}$  8.1 Hz,  $J_{1',2}$  6.6 Hz, H-1'), 3.37 (1H, d,  $J$  13.2 Hz, NCH<sub>2</sub>Ph), 3.92 (1H, d,  $J$  13.2 Hz, NCH<sub>2</sub>Ph), 4.23 (1H, dd,  $J_{5,5'}$  11.5 Hz,  $J_{5,4}$  4.3 Hz, H-5), 4.27 (1H, dd,  $J_{5',5}$  11.5 Hz,  $J_{5',4}$  5.9 Hz, H-5'), 4.82 (1H, dddd,  $J_{2,1}$  10.7 Hz,  $J_{2,1'}$  6.6 Hz,  $J_{2,3}$  5.5 Hz,  $J_{2,NH}$  8.6 Hz, H-2), 5.26 (1H, dd,  $J_{3,2}$  5.5 Hz,  $J_{3,4}$  1.5 Hz, H-3), 5.42 (1H, d,  $J_{NH,2}$  8.6 Hz, NH), 7.25–7.35 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, C<sub>6</sub>D<sub>6</sub>) 20.7, 20.7 (2 × OC(O)CH<sub>3</sub>), 22.9 (NHC(O)CH<sub>3</sub>), 49.3 (C-2), 55.6 (C-1), 59.1 (NCH<sub>2</sub>Ph), 63.5 (C-5), 68.8 (C-4), 76.4 (C-3), 127.7, 128.8, 129.3 (CH(Ar)), 138.9 (C(Ar)), 168.9, 169.4, 170.6 (3 × C=O);  $m/z$  HRMS (ESI<sup>+</sup>): Found 349.1756, C<sub>18</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> requires 349.1763.

The enantiomeric triacetate **22D**, oil;  $[\alpha]_D^{23} -77.7$  (c 0.65, CHCl<sub>3</sub>), was prepared by a similar method. All other physical data was identical to that of **22L**.

## 13. 2-Acetamido-*N*-benzyl-1,4-imino-1,2,4-trideoxy-*L*-ribitol (*N*-benzyl-LRBNAc) **13L**

Sodium methoxide (3.2 mg, 0.059 mmol) was added to a stirred solution of the triacetate **22L** (103 mg, 0.296 mmol) in methanol (1.0 mL) at room temperature under an atmosphere of nitrogen. After 2 h, analysis by TLC (acetone) showed no residual starting material ( $R_f$  0.55) and a spot due to the product ( $R_f$  0.29). The solvents were removed *in vacuo* and the resulting residue was purified by flash chromatography (ethyl acetate, then acetone) to give the *N*-benzyl-acetamide **13L** (71.1 mg, 91%) as a pale yellow oil that was recrystallised from acetonitrile, m.p. (acetonitrile) 81–82 °C;  $[\alpha]_D^{22} +76.8$  (c 0.72, MeOH);  $\nu_{\max}$  (NaCl) 3318 (O-H and N-H), 1643 (C=O amide band I), 1551 (N-H amide band II) cm<sup>-1</sup>;  $\delta_H$ (400 MHz, CD<sub>3</sub>CN): 1.86 (3H, s, amide CH<sub>3</sub>), 2.29 (1H, dd,  $J_{1,1'}$  8.3 Hz,  $J_{1,2}$  10.3 Hz, H-1), 2.34 (1H, br s, OH), 2.61 (1H, dt,  $J_{4,3}$  2.3 Hz,  $J$  4.0 Hz, H-4), 2.92 (1H, dd,  $J_{1',1}$  8.3 Hz,  $J_{1',2}$  6.5 Hz, H-1'), 3.44–3.49 (3H, m, H-5, H-5', NCH<sub>2</sub>Ph), 3.94 (1H, d,  $J$  13.1 Hz, NCH<sub>2</sub>Ph), 3.99 (1H, dd,  $J_{3,2}$  5.7 Hz,  $J_{3,4}$  2.3 Hz, H-3), 4.01–4.09 (1H, m, H-2), 6.49 (1H, d,  $J_{NH,2}$  5.7 Hz, amide NH), 7.21–7.36 (5H, m, CH(Ar));  $\delta_C$ (100 MHz, CD<sub>3</sub>CN) 22.5 (NHC(O)CH<sub>3</sub>), 51.2 (C-

2), 55.9 (C-1), 59.0 (NCH<sub>2</sub>Ph), 61.8 (C-5), 73.0 (C-3), 73.5 (C-4), 127.4, 128.6, 129.2 (CH(Ar)), 139.7 (C(Ar)), 170.5 (C=O); *m/z* HRMS (ESI<sup>+</sup>): found 265.1556, C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> requires 265.1552. Found: C, 63.74; H, 7.64; N, 10.62; C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> requires C, 63.62; H, 7.63; N, 10.60%.

The enantiomeric acetamide **13D**, oil; [ $\alpha$ ]<sub>D</sub><sup>23</sup> –74.3 (c 0.79, MeOH), was prepared by a similar method. All other physical data was identical to that of **13L**.

#### 14. 2-Acetamido-1,4-imino-1,2,4-trideoxy-L-ribitol (LRBNAC) **12L**

Palladium black (10.0 mg) was added to a stirred solution of *N*-benzyl derivative **13L** (40.0 mg, 0.151 mmol) in 1,4-dioxane (0.5 mL) and water (0.5 mL) at room temperature under an atmosphere of H<sub>2</sub>. After 18 h, analysis by TLC (acetone) showed no residual starting material (*R*<sub>f</sub> 0.15) and a spot due to the product on the baseline. The palladium black was filtered off over Celite<sup>®</sup>, washing with methanol. The solvents were removed *in vacuo* and the remaining residue was purified by ion-exchange chromatography (Dowex<sup>®</sup> 50WX8-200) to afford LRBNAC **12L** (23.3 mg, 88%) as an orange oil; [ $\alpha$ ]<sub>D</sub><sup>22</sup> +31.4 (c 0.36, H<sub>2</sub>O);  $\nu_{\max}$  (Ge) 3289 (O-H and N-H), 1651 (C=O amide band I), 1554 (N-H amide band II) cm<sup>-1</sup>;  $\delta_{\text{H}}$ (400 MHz, D<sub>2</sub>O) 1.91 (3H, s, COCH<sub>3</sub>), 2.75 (1H, dd, *J*<sub>1,1'</sub> 11.4 Hz, *J*<sub>1,2</sub> 8.6 Hz, H-1), 3.07 (1H, a-dt, *J*<sub>4,3</sub> 5.0 Hz, *J* 5.4 Hz, H-4), 3.19 (1H, dd, *J*<sub>1,1'</sub> 11.4 Hz, *J*<sub>1,2</sub> 7.0 Hz, H-1'), 3.55 (1H, dd, *J*<sub>5,5'</sub> 11.8 Hz, *J*<sub>5,4</sub> 5.8 Hz, H-5), 3.61 (1H, dd, *J*<sub>5',5</sub> 11.8 Hz, *J*<sub>5',4</sub> 5.0 Hz, H-5'), 3.97 (1H, dd, *J*<sub>3,2</sub> 6.0 Hz, *J*<sub>3,4</sub> 5.0 Hz, H-3), 4.09 (1H, a-dt, *J*<sub>2,1</sub> 8.6 Hz, *J* 6.5 Hz, H-2);  $\delta_{\text{C}}$ (100 MHz, D<sub>2</sub>O) 22.1 (NHCOCH<sub>3</sub>), 48.0 (C-1), 52.3 (C-2), 61.5 (C-5), 65.8 (C-4), 71.5 (C-3), 174.7 (C=O); *m/z* HRMS (ESI<sup>+</sup>): found 175.1078, C<sub>7</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> requires 175.1083.

The enantiomeric DRBNAC **12D**, oil; [ $\alpha$ ]<sub>D</sub><sup>22</sup> –27.2 (c 0.34, H<sub>2</sub>O), was prepared by a similar method. All other physical data was identical to that of DRBNAC **12L**.

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