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Looking glass inhibitors: efficient synthesis and biological evaluation of D-deoxyfuconojirimycin

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Abstract—1,6-Dideoxygalactostatin, the mirror image of 1-deoxy-L-fuconojirimycin, was efficiently prepared from 2,3-*O*-isopropylidene-L-lyxonolactone in four steps and evaluated as a glycosidase inhibitor.

Keywords: Galactostatin; Glycosidase inhibitor; 1-Deoxyfuconojirimycin; Iminosugar; Mirror image

1. Introduction

Iminosugars can be viewed as sugar mimics in which the ring oxygen atom of the parent sugar has been replaced by nitrogen. Such compounds have been the subject of extensive interest in the past three decades due to their therapeutic potential.[1] Some of them have already been tested or approved in the treatment of diabetes,[2] Gaucher's disease,[3] HIV infection,[4] viral infections[5] or cancer.[6] They have also been used as chemical probes, in combination with protein crystallography and kinetics studies, to provide new insights into glycosidase mechanism.[7]

Although the quest for stronger glycosidase inhibitors has been the driving force for the synthetic efforts dedicated to this class of compounds,[8] it is probable that several of their biological properties are not related to their ability to inhibit glycosidases.[9] Even apparent mimics of sugars act as mimics of other compounds, such as ceramide.[10]

Among iminosugar piperidine analogues,[11] L-DFJ (L-deoxyfuconojirimycin) (−)-**1** (Chart 1), a L-fucose analogue, is one of the most powerful glycosidase inhibitor reported to date, displaying K_i values in the low nanomolar range.[12] Looking glass inhibitors[13] [the enantiomers of the naturally occurring glycosidase inhibitors] often have significant glycosidase inhibition profiles and thus also have therapeutic potential.[14] We were thus particularly interested in D-DFJ (+)-**1**, the mirror image of L-DFJ (−)-**1**, a 1,6-dideoxy analogue of the natural product galactostatin **2**[15] because some of its *N*-alkyl derivatives have recently displayed very promising biological properties.[16] The *N*-nonyl derivative **3** (Chart 1) has been shown to dramatically reduce the amount of hepatitis B virus (HBV) produced by tissue cultures under conditions where cell viability is not affected[17] while the *N*-oxanonyl derivative **4** (Chart 1) was proved to block the protein p7 ion channels of hepatitis C virus.[18] Furthermore, compound **4** showed very low toxicity in mice, rats and dogs unlike deoxynojirimycin derivatives interacting with glucose-metabolising enzymes and displaying unwanted side effects. The

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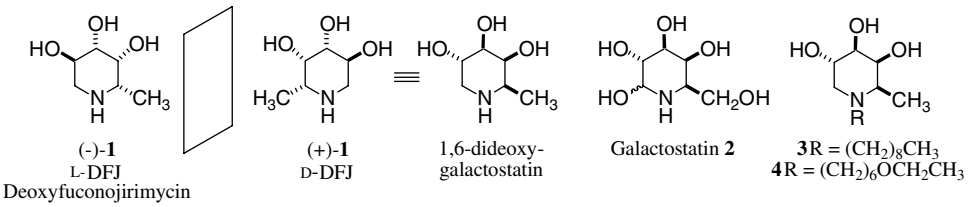


Chart 1. Structures of L-DFJ (−)-**1**, D-DFJ (+)-**1**, galactostatin **2** and derivatives **3** and **4**.

N-oxanonyl 1,6-dideoxygalactostatin **4** has entered into phase I clinical studies in July 2002.

Four approaches to 1,6-dideoxygalactostatin (+)-**1** have been reported so far including a chemo-enzymatic approach,[19] an asymmetric hetero Diels–Alder cycloaddition,[20] an oxime derivative cyclisation[21] and a strategy using a 6-deoxy-hex-5-enopyranosyl azide as the key compound.[22] Our group has previously published a preliminary communication on the synthesis of L-DFJ from D-lyxonolactone using only a single isopropylidene protecting group.[23] This article provides a full experimental improved procedure (applicable to large scale) for the synthesis of L-DFJ (−)-**1** and its enantiomer D-DFJ (+)-**1** from D- and L-lyxonolactone, respectively, and also includes evaluation of D-DFJ (+)-**1** as a glycosidase inhibitor.

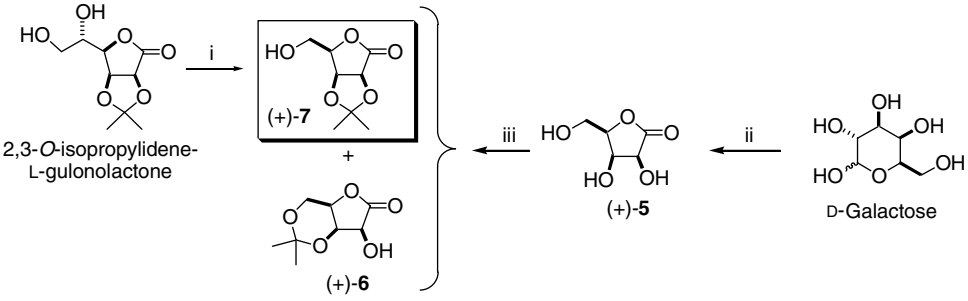
2. Results and discussion

In our previous approach to L-DFJ (−)-**1**, D-lyxonolactone (+)-**5** was prepared by the Humphlett procedure[24] from D-galactose and was then treated with acetone in the presence of anhyd copper sulfate to afford, along with some 3,5-*O*-isopropylidene-D-lyxonolactone (+)-**6**, the desired 2,3-*O*-isopropylidene-D-lyxonolactone (+)-**7** in 60% yield. An improved route to compound (+)-**7** was devised starting from readily available 2,3-*O*-isopropylidene-L-gulonolactone,[25] which upon treatment with periodic acid yielded the corresponding aldehyde, which was reduced to the alcohol with sodium cyanoborohydride to afford 2,3-*O*-isopropylidene-D-lyxonolactone (+)-**7** in 84% yield (Scheme 1).

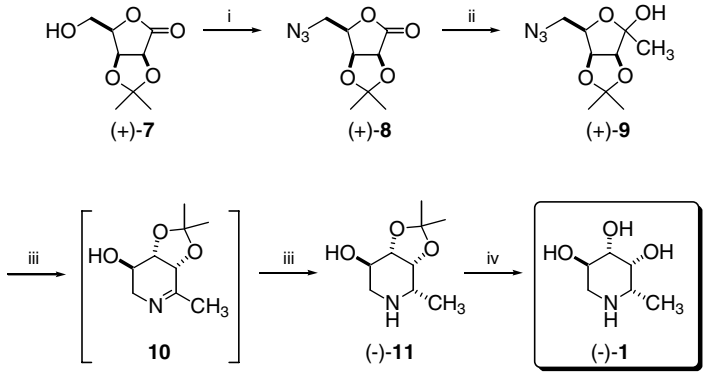
The sequence was then identical to the one previously reported.[23] Triflation of the free alcohol in compound (+)-**7** followed by azide displacement afforded the corresponding azidolactone (+)-**8** in 89% yield. Methyl lithium addition gave the corresponding azidolactol (+)-**9** in 97% yield. Hydrogenation of compound (+)-**9** afforded iminofucitol (−)-**11** in 91% yield via formation of imine **10**. Final deprotection gave deoxyfuconojirimycin (−)-**1** after purification, identical with an authentic sample (Scheme 2).

The synthesis of D-DFJ (+)-**1** was undertaken by analogy with that used for the synthesis of L-DFJ (−)-**1**, starting from 2,3-*O*-isopropylidene L-lyxonolactone (−)-**7**[26] obtained from the readily available 2,3-*O*-isopropylidene-D-gulonolactone (Scheme 3).

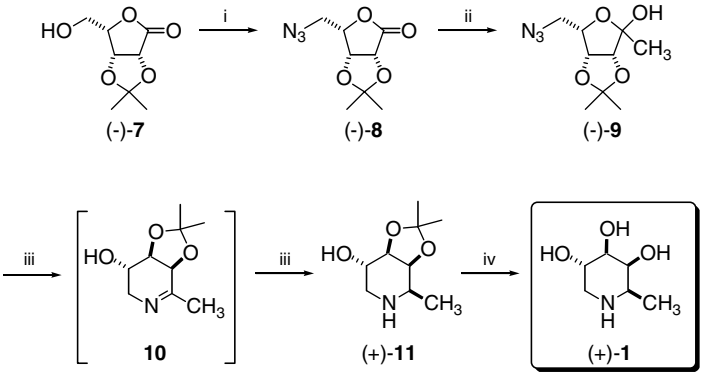
Esterification of the free hydroxyl group in compound (−)-**7** with trifluoromethanesulfonic anhydride in dichloromethane followed by nucleophilic displacement of the resulting triflate with sodium azide in DMF gave the corresponding azidolactone (−)-**8** in 88% yield. Introduction of the methyl group was achieved by methyl lithium addition to azidolactone (−)-**8** in THF at −78 °C to afford azidolactol (−)-**9** as a single stereoisomer in 91% yield. The stereochemistry of the new chiral centre was not determined (in a similar case, it has been established that the product is derived from alkyl lithium attack from the more hindered face).[27] Hydrogenation of azidolactol (−)-**9** in the presence of palladium black in EtOH resulted in reduction of the azide to the corresponding amine followed by intramolecular reductive amination to give the protected imine intermediate **10**, which was subsequently reduced to exclusively afford the corresponding protected iminosugar (+)-**11** in 84%



Scheme 1. Different routes to 2,3-*O*-isopropylidene-D-lyxonolactone (+)-**7**. Reagents and conditions: (i) periodic acid, $NaBH_3CN$, THF, 84% yield; (ii) Ref. 23; (iii) anhyd $CuSO_4$, acetone, 81%.



Scheme 2. Synthesis of deoxyfuconojirimycin (−)-**1**. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2 then NaN_3, DMF, 89% yield; (ii) MeLi, THF, MS 4 Å, −78 °C, 97% yield; (iii) H_2, Pd black, EtOH, 91% yield; (iv) 50% aq TFA, 98% yield.



Scheme 3. Synthesis of 1,6-dideoxy-galactostatin (+)-**1**. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2 then NaN_3, DMF, 88% yield; (ii) MeLi, THF, MS 4 Å, −78 °C, 91% yield; (iii) H_2, Pd black, EtOH, 84% yield; (iv) 50% aq TFA, 96% yield.

yield. The stereochemistry of the reduction of the transient imine is controlled by the adjacent isopropylidene group. Treatment of compound (+)-**11** with aq trifluoroacetic acid afforded the target D-DFJ (+)-**1** in 96% yield, which displayed spectroscopic data consistent with those reported in the literature.[20,21] This short sequence from readily available 2,3-*O*-isopropylidene D-gulonolactone may be readily carried out on a multigram scale to afford the target iminosugar (+)-**1** in a competitive 54% overall yield.

Iminosugar (+)-**1** was further evaluated as a glycosidase inhibitor on various galactosidases and fucosidases (Table 1) and compared to galactostatin. Deoxygenation of C-6 in the galactose mimic (+)-**1** reduces the inhibitory potency for α-galactosidases and β-galactosidases significantly as expected. Interestingly, compound (+)-**1** was found to be a moderate inhibitor of naringinase, a glycosidase, which targets L-rhamnose containing saccharides.

In summary, we have achieved a straightforward synthesis of 1,6-dideoxy-galactostatin (+)-**1**, the enantiomer of the potent fucosidase inhibitor deoxyfuconojirimycin (−)-**1**, in five steps from L-lyxonolactone and in 54% overall yield. This compound displays moderate glycosidase inhibition on several plant and human α- and β-galactosidases but has since been proved to have promising therapeutic potential as its *N*-alkyl derivatives.

Table 1. Inhibition data of iminosugar (+)-**1** and galactostatin[28] on various glycosidases

	Enzyme						
	Coffee bean α-galactosidase	Human liver α-galactosidase	Human liver β-galactosidase	Jack bean β-galactosidase	Human liver α-L-fucosidase	Human liver α-arabinosidase	Naringinase
(+)-**1**	1.36 μM	46 μM	19%	28%	50%	5%	90 μM*
Galactostatin	3.1 nM	0.32 μM	93%	5.2 μM*	97%	69%	23%

Inhibition values reported are expressed as K_i, IC_{50}* or % of inhibition at 1 mM concentration.

3. Experimental

3.1. General methods

Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Bruker AM 500 (500 MHz) spectrometer. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz), Bruker AC 200 (50 MHz) or Bruker AM 500 (125 MHz) spectrometer and multiplicities were assigned using a DEPT sequence. The following abbreviations are used to explain multiplicities; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Infrared spectra were recorded on a Perkin–Elmer 1750 FTIR infrared spectrophotometer. Mass spectra were recorded on a VG Masslab 20–250, BIO-Q by desorption chemical ionisation (DCI, NH_3), chemical ionisation (CI, NH_3), electrospray or thermospray, or atmospheric pressure chemical ionisation (APCI+ or APCI−) as stated. High resolution mass spectra (HRMS) were recorded on a VG Autospec mass spectrometer using chemical ionisation. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. Microanalyses were performed by the microanalysis services of the Dyson Perrins Laboratory and the Inorganic Chemistry Laboratory, Oxford. Thin layer chromatography (TLC) was carried out on plastic or aluminium sheets coated with $60F_{254}$ silica and developed using a spray 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica gel. Solvents and commercially available reagents were dried and purified before use according to standard procedures; hexane was distilled at 68 °C before use to remove less volatile fractions.

3.1.1. 2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone (−)-7. 2,3-*O*-Isopropylidene-D-gulonolactone (10.9 g, 50 mmol) was dissolved in dry THF (250 mL) under N_2. Periodic acid (12.8 g, 56 mmol) was added. After 5 min, the soln became cloudy and was vigorously stirred for another 15 min. The reaction mixture was purified by elution through a silica plug eluted with EtOAc. The solvent was removed under diminished pressure to afford a yellow oil, which was dissolved in AcOH (150 mL). Sodium cyanoborohydride (3.22 g, 51 mmol) was added and the soln stirred for 90 min. A soln of satd aq ammonium chloride (20 mL) was added to quench the reaction mixture and the solvent was removed under diminished pressure. The residue was dissolved in EtOAc (200 mL) and washed with a satd aq ammonium chloride soln (50 mL), water (50 mL) and brine (50 mL). The aq layer was re-extracted with EtOAc (3 × 50 mL). The organic fractions were combined, dried (magnesium sulfate), filtered and the solvent removed. Purification by flash chromatography (EtOAc) gave 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (−)-**7** (7.93 g, 42 mmol, 84% yield) as a white crystalline solid.

Mp 94–95 °C; $[\alpha]_D^{23}$ −90.8 (*c* 1.08, acetone) (lit.:[26] −85.6; *c* 1, acetone); ^1H NMR (500 MHz, $CDCl_3$): 1.41, 1.49 (6H, 2 × s, $C(CH_3)_2$), 2.18 (1H, br, OH), 3.87 (1H, dd, $J_{4,5'}$ 5.3 Hz, $J_{5,5'}$ 12.3 Hz, H-5′), 4.15 (1H, dd, $J_{4,5}$ 6.4 Hz, H-5), 4.56 (1H, ddd, $J_{3,4}$ 3.6 Hz, H-4), 4.82 (1H, d, $J_{2,3}$ 5.5 Hz, H-2), 4.85 (1H, dd, H-3), ^{13}C NMR (50 MHz, $CDCl_3$): 26.2 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 61.3 (CH_2, C-5), 76.6, 76.7, 79.8 (3 × CH, C-2, C-3, C-4), 114.9 ($C(CH_3)_2$), 174.3 (C=O). Physical data for enantiomer (+)-**7**: Mp 97–98 °C; $[\alpha]_D^{22}$ +92.3 (*c* 0.37, acetone).[28]

3.1.2. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (−)-8. 2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone (−)-**7** (5.8 g, 30.9 mmol) was dissolved in anhyd CH_2Cl_2 (140 mL) under N_2. The soln was cooled to −30 °C and dry pyridine (12 mL) was added. Trifluoromethanesulfonic anhydride (6.5 mL, 38.7 mmol) was then added dropwise to the soln, which was stirred at −30 °C. After 1 h, TLC (1:1 EtOAc/hexane) showed a complete reaction. The soln was allowed to warm to 0 °C and dry DMF (250 mL) and sodium azide (8.2 g, 126 mmol) were added. The suspension was stirred at room temperature for 4 h. Water (25 mL) was added to quench the reaction. The solvent was then removed under diminished pressure and co-evaporated with toluene. The residue was dissolved in CH_2Cl_2 (250 mL) and washed with water (2 × 50 mL) and brine (50 mL). The aq layer was re-extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined, dried (magnesium sulfate), filtered and the solvent removed. Purification by flash chromatography (1:1 hexane/EtOAc) afforded 5-azido-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (−)-**8** (5.8 g, 27.2 mmol, 88% yield) as white crystals.

Mp 58–59 °C; $[\alpha]_D^{23}$ −71.0 (*c* 2.0, $CHCl_3$); ν_{max} (film) 1784 (C=O), 2101 cm^{-1} (N_3); ^1H NMR (500 MHz, $CDCl_3$): 1.42, 1.50 (6H, 2 × s, $C(CH_3)_2$), 3.66 (1H, dd, $J_{4,5'}$ 6.3 Hz, $J_{5,5'}$ 12.9 Hz, H-5′), 3.72 (1H, dd, $J_{4,5}$ 7.1 Hz, H-5), 4.62 (1H, ddd, $J_{3,4}$ 3.5 Hz, H-4), 4.83 (1H, dd, $J_{2,3}$ 5.4 Hz, H-3), 4.86 (1H, d, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): 26.3 ($C(CH_3)_2$), 26.5 ($C(CH_3)_2$), 50.4 (CH_2, C-5), 76.1, 76.4, 77.6 (3 × CH, C-2, C-3, C-4), 115.1 ($C(CH_3)_2$), 173.4 (s, C=O); *m*/*z* (CI, NH_3): 218 (100%), 186 (35%, MH^+-N_2); Anal. Calcd for $C_8H_{11}O_4N_3$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.26; H, 5.43; N, 19.24. Physical data for enantiomer (+)-**8**: Mp 59.7 °C; $[\alpha]_D^{23}$ +72 (*c* 1, $CHCl_3$).[23]

3.1.3. 6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene-L-lyxo-2-hexulofuranose (−)-9. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (−)-**8** (4 g, 18.8 mmol)

was dissolved in dry THF (70 mL) under N_2 in the presence of 4 Å molecular sieves. The soln was cooled to −78 °C. Methyl lithium (18 mL, 25.2 mmol, 1.4 M soln in diethyl ether) was added and the soln stirred at −78 °C. After 2 h, TLC (1:1 EtOAc/hexane) showed no starting material (R_f 0.62) and a new product (R_f 0.72). A satd aq ammonium chloride soln (10 mL) was added and the soln was stirred for 30 min. The reaction mixture was then extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts were combined, dried (magnesium sulfate), filtered off and the solvent removed under diminished pressure. The resulting yellow solid was purified by flash chromatography (1:2 EtOAc/hexane) to give 6-azido-1,6-dideoxy-3,4-*O*-isopropylidene-L-lyxo-2-hexulofuranose (−)-**9** (3.49 g, 91% yield) as a white solid.

Mp 89–90 °C; $[\alpha]_D^{21}$ −12.5 (*c* 1, $CHCl_3$); ν_{max} (KBr): 3436 (br, OH), 2101 cm^{-1} (N_3); ^1H NMR (500 MHz, $CDCl_3$): 1.33, 1.48 (6H, 2 × s, $C(CH_3)_2$), 1.54 (3H, s, CH_3), 2.13 (1H, br, OH), 3.54 (2H, d, $J_{6,6'}$ 6.4 Hz, H-6, H-6′), 4.23 (1H, app. dt, $J_{5,4}$ 3.9 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.48 (1H, d, $J_{3,4}$ 5.9 Hz, H-3), 4.78 (1H, dd, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): 22.9 (CH_3, C-1), 25.2, 26.5 (2 × CH_3, $C(CH_3)_2$), 50.4 (CH_2, C-6), 77.9, 80.9, 85.8 (3 × CH, C-3, C-4, C-5), 105.9 (C-2), 113.4 ($C(CH_3)_2$); *m*/*z* (APCI+): 216 (92%), 202 (MH^+-N_2, 38%), 184 ($MH^+-H_2O-N_2$, 100%); Anal. Calcd for $C_9H_{15}O_4N_3$: C, 47.16; H, 6.60; N, 18.33. Found: C, 47.38; H, 6.53; N, 18.03. Physical data for enantiomer (+)-**9**: Mp 86–87 °C; $[\alpha]_D^{23}$ +16 (*c* 1, $CHCl_3$).[23]

3.1.4. 1,5-Imino-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-galactitol (+)-11. 6-Azido-1,6-dideoxy-3,4-*O*-isopropylidene-L-lyxo-2-hexulofuranose (−)-**9** (1.0 g, 4.4 mmol) was dissolved in EtOH (25 mL). Palladium black (300 mg) was added. The soln was degassed three times and air was replaced by H_2. The soln was stirred at room temperature under an atmosphere of H_2. After 24 h, the soln was filtered through a Celite plug eluted with EtOH. The solvent was removed under diminished pressure to give a yellow solid, which was purified by flash chromatography (4:1 $CHCl_3$/MeOH) to afford 1,5-imino-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-galactitol (+)-**11** as a white solid (700 mg, 3.7 mmol, 84% yield).

Mp 164–166 °C; $[\alpha]_D^{22}$ +84.0 (*c* 1, $CHCl_3$); ν_{max} (KBr): 3434 cm^{-1} (br, OH, NH); ^1H NMR (500 MHz, $CDCl_3$): 1.27 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3), 1.38, 1.55 (6H, 2 × s, $C(CH_3)_2$), 1.95 (1H, br, OH), 2.48 (1H, dd, $J_{1a,2}$ 10.6 Hz, $J_{1e,1a}$ 13.0 Hz, H-1a), 3.08 (1H, dq, $J_{4,5}$ 2.6 Hz, H-5), 3.12 (1H, dd, $J_{1e,2}$ 5.1 Hz, H-1e), 3.67 (1H, ddd, $J_{2,3}$ 7.1 Hz, H-2), 3.88 (1H, dd, $J_{3,4}$ 5.3 Hz, H-3), 4.04 (1H, dd, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): 18.0 (CH_3, C-6), 26.7, 28.7 (2 × CH_3, $C(CH_3)_2$), 48.7 (CH_2, C-1), 51.6 (CH, C-5), 71.1, 77.0, 80.5 (3 × CH, C-2, C-3, C-4), 109.5 ($C(CH_3)_2$); *m*/*z* (APCI+): 188 (MH^+, 100%), 130 (19%); Anal. Calcd for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found C, 57.26; H, 9.40; N, 7.24. HRMS: Calcd for MH^+: 188.1286; Found: 188.1278. Physical data for enantiomer (−)-**11**: Mp 183–184 °C; $[\alpha]_D^{23}$ −77 (*c* 1, $CHCl_3$).[23]

3.1.5. 1,5-Imino-1,5,6-trideoxy-D-galactitol (+)-1. 1,5-Imino-3,4-*O*-isopropylidene-1,5,6-trideoxy-D-galactitol (+)-**11** (133 mg, 0.71 mmol) was dissolved in 50% aq trifluoroacetic acid (4 mL) and the soln was stirred for 2 h. The solvent was removed under diminished pressure and co-evaporated with toluene (2 × 5 mL). Purification by flash chromatography (20:77:3 $CHCl_3$/CH_3OH/MeOH/conc NH_3 soln) afforded 1,5-imino-1,5,6-trideoxy-D-galactitol (+)-**1** (102 mg, 96% yield), which was freeze-dried to give a brown foam.

$[\alpha]_D^{24}$ +42.2 (*c* 0.66, H_2O) (lit.:[20] +49; *c* 1, H_2O); ν_{max} (film): 3370 cm^{-1} (br, OH, NH); ^1H NMR (500 MHz, MeOH-d^4): 1.17 (3H, d, $J_{5,6}$ 6.7 Hz, CH_3), 2.40 (1H, dd, $J_{1a,2}$ 10.9 Hz, $J_{1a,1e}$ 12.8, H-1a), 2.80 (1H, dq, $J_{5,4}$ <0.5 Hz, H-5), 3.08 (1H, dd, $J_{1e,2}$ 5.3 Hz, H-1e), 3.33 (1H, m, H-3), 3.75–3.70 (2H, m, H-2, H-4); ^{13}C NMR (125 MHz, MeOH-d^4): 15.7 (q, CH_3), 49.4 (t, CH_2) 54.0 (d, C-5), 67.6, 72.2, 75.7 (3 × d, C-2, C-3, C-4); *m*/*z* (APCI+): 148 (MH^+, 100%); HRMS: Calcd for MH^+: 148.0973; Found: 148.0968. Physical data for enantiomer (−)-**1**: $[\alpha]_D^{23}$ −48.8 (*c* 0.64, H_2O).[23]

Acknowledgements

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