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Bioorganic & Medicinal Chemistry 12 (2004) 225–232
Bioorganic & Medicinal Chemistry

Syntheses of tetrahydroxyazepanes from *chiro*-inositols and their evaluation as glycosidase inhibitors

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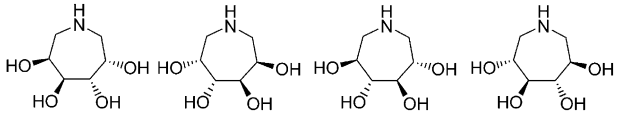
Received 4 September 2003; accepted 5 October 2003

Abstract—Two pairs of C_2-symmetric tetrahydroxyazepanes [(−), (+)-**1** and (−), (+)-**2**] have been synthesized from the enantiomeric *chiro*-inositols and evaluated as glycosidase inhibitors. Alternative syntheses of *ido*-tetrahydroxyazepanes (−)- and (+)-**2** from *myo*-inositol were also developed. The key synthetic transformations were glycol fission and cyclization of the derived dialdehydes by double reductive amination. The D-*manno*-tetrahydroxyazepane [(−)-**1**] showed selective inhibition of α-L-fucosidase and β-D-galactosidase, while the enantiomer [(+)-**1**] was a selective inhibitor of an α-D-galactosidase. In contrast, the L-*ido*-tetrahydroxyazepane (+)-**2** was a broad spectrum hexosidase inhibitor, but showed none of the reported hexosaminidase inhibition. Its enantiomer (−)-**2** is a poor hexosidase inhibitor.

1. Introduction

Iminosugars, having nitrogen as the ring hetero-atom instead of oxygen, and their derivatives have been widely studied inhibitors of oligosaccharide processing enzymes such as glycosidases and glycosyltransferases[1,2] which are involved in the biosynthesis of the epitopes responsible for various biological molecular recognition events linked to diseases such as diabetes[3] and cancer.[4,5] Of the large number of such inhibitors developed, both as molecular probes and potential therapeutic agents,[2] five- and six-membered iminosugar derivatives, notably the 1-deoxy analogues, have received most attention, and relatively few reports have appeared on the inhibitory activities of the seven-membered analogues.[6–13] While the six-membered 1-deoxy-iminosugars are generally selective inhibitors of the enzymes that cleave the pyranosyl glycosides with the same configurations,[14,15] this correlation is less reliable for seven-membered analogues which can be attributed, at least in part, to the increased flexibility of polyhydroxylated azepanes.[11]

We have been interested in the use of the enantiomeric *chiro*-inositols as starting materials for the synthesis of polyhydroxylated chiral compounds,[16a] because both enantiomers are readily available, which is not the case for most alternative starting materials such as the hexoses. Previously we reported the synthesis of the D-*manno*-(−)-**1** and L-*manno*-(+)-**1** tetrahydroxyazepanes from these starting materials,[17] and now extend this approach to the D- and L-*ido*-isomers (−)-**2** and (+)-**2.** The inhibitory properties of the four tetrahydroxyazepanes against eight glycosidases are also reported.



2. Results and discussion

In the previous study azepanes (−)-**1** and (+)-**1** were synthesized from D- and L-*chiro*-inositol, respectively,[17] by *cis*-α-diol protection, oxidative *trans*-diol fission,[18] reductive amination of the dialdehyde formed to give the azepane,[19,20] and deprotection. In this way, D-*chiro*-inositol was converted to (−)-**1** via (+)-**3**, (−)-**4** and (−)-**5** (Fig. 1).

Preparation of the *ido*-configured azepanes (−)- and (+)-**2** utilizing similar methodology requires selective protection of the four equatorial hydroxyl groups of L- and D-*chiro*-inositol, respectively. This was achieved by reaction with butan-2,3-dione and trimethylorthoformate in the presence of camphorsulfonic acid, a procedure

Keywords: Iminosugar; Glycosidase inhibition; Synthesis; Inositols.
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doi:10.1016/j.bmc.2003.10.003

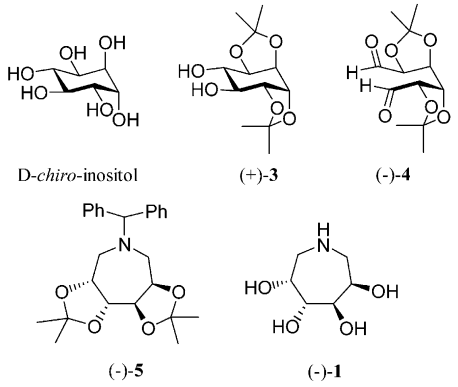


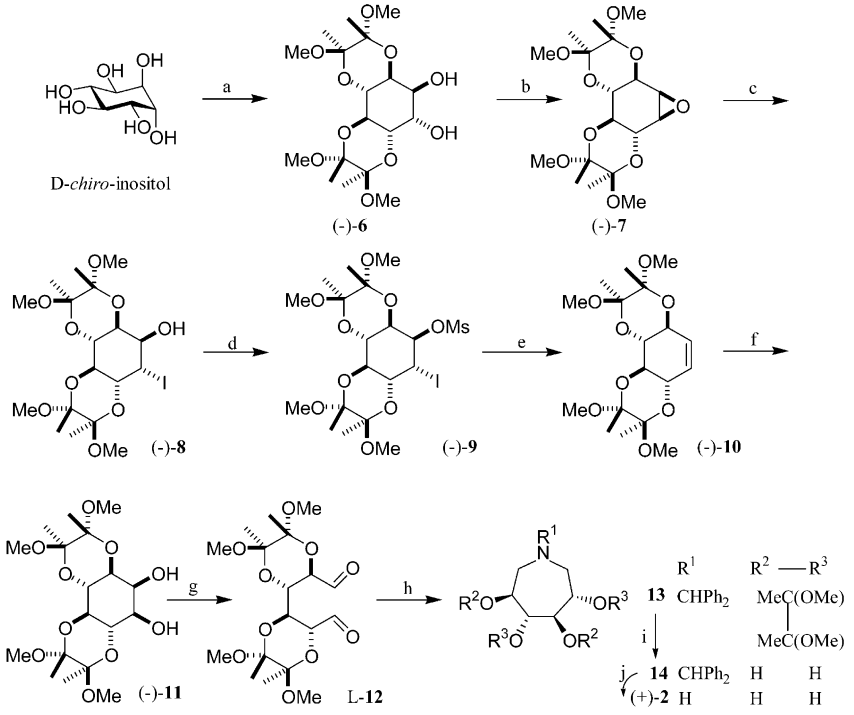
Figure 1.

known to favor the protection of 1,2-diequatorial *trans*-diols on six-membered rings,[21] and the products were used to give the *ido*-compounds **2** as illustrated for the conversion of D-*chiro*-inositol to (+)-**2** in Scheme 1. Although the ^{1}H NMR spectrum of the first intermediate (−)-**6**[16b] did not allow the conclusion that its diol was diaxial, it is expected to be so given the propensity of the oxygen atoms of the dioxane rings to be equatorial. Attempted oxidative fission of the presumed *trans*-diaxial vicinal diol moiety of the diacetal (−)-**6** with sodium periodate or lead tetraacetate under various reaction conditions failed. Since cleavage of vicinal diols with periodate involves cyclic iodine-containing intermediates which cannot be formed from *trans*-diols locked in the diaxial orientation on six-membered rings, such diols, for example methyl 4,6-*O*-benzylidene-α-D-altropyranoside, are stable towards this reagent.[22]

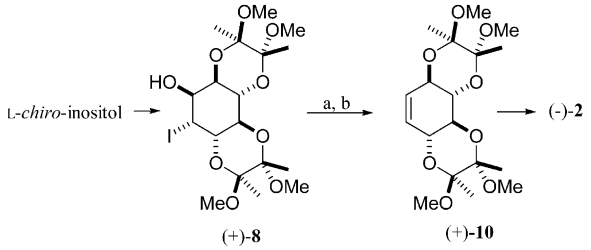
D-*chiro*-Inositol-based *trans*-diol (−)-**6** consequently had to be modified before it could be used for the preparation of azepanes. By Mitsunobu epoxide formation[23] it was converted into the *myo*-inositol derivative (−)-**7**, epoxide ring opening with iodide ion gave (−)-**8**, mesylation [to (−)-**9**] and reductive elimination led to alkene (−)-**10** which was *cis*-dihydroxylated. The epoxide opening step occurred with high selectivity to give the diaxial product (−)-**8** in keeping with the Fürst Plattner rule,[24] and *cis*-dihydroxylation from either face of symmetrical alkene (−)-**10** gave the *myo*-inositol diol (−)-**11.** Attempts to form the *myo*-inositol diol (−)-**11** directly from its isomer (−)-**6** by epimerization under various Mitsunobu conditions led only to epoxide (−)-**7**, and the dimesylate and the ditriflate of the diol gave only small yields of the alkene (−)-**10** under reductive elimination conditions. Oxidative fission of the *cis*-diol (−)-**11** proceeded readily to afford dialdehyde L-**12** in near quantitative yield, and reductive amination of this product, followed by deprotection, afforded the previously reported tetrahydroxyazepane (+)-**2** (Scheme 1).[7–12]

The previously unreported D-*ido*-azepane (−)-**2** was prepared in similar manner starting from L-*chiro*-inositol. The best method found for the production of alkene (+)-**10** was 'one-pot' triflation of iodo-alcohol (+)-**8** followed by reduction (Zn-dust, AcOH) (Scheme 2). In this way the alkene (+)-**10** was obtained from (+)-**8** in 95% yield, this approach representing a significant improvement over the elimination process illustrated in Scheme 1.

An alternative synthesis of (+)-**2** was developed from the known tetra-*O*-benzyl-*myo*-inositol (−)-**15.**[25] Oxidative

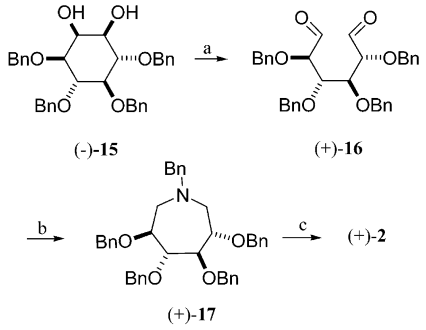


Scheme 1. Reagents and conditions: (a) butanedione, $CH(OMe)_3$, H^+, MeOH, reflux (80%); (b) Ph_3P, DEAD, THF, 0 °C (68%); (c) $AlCl_3$, MeCN, NaI, 0 °C (95%); (d) MsCl, Et_3N, CH_2Cl_2 (57%); (e) Zn dust, AcOH, DMF, 80 °C (92%); (f) $NaIO_4$, $RuCl_3$, EtOAc, MeCN, H_2O (98%); (g) $NaIO_4$, activated silica, CH_2Cl_2 (90–95%); (h) $NaCNBH_3$, MeOH, $(Ph)_2CHNH_2$, 3 Å sieves, 78 °C–rt; (i) TFA, H_2O; (j) H_2, $Pd(OH)_2$/C, MeOH (h–j), 42%.



Scheme 2. (a) Tf_2O, Py, DMF; (b) Zn, AcOH (95%).

fission with periodate afforded dialdehyde (+)-**16** that was subjected directly to reductive amination (Scheme 3). In this case, $NaBH(OAc)_3$ and benzylamine proved superior to $NaCNBH_3$ for the latter process. The pentabenzyl azepane (+)-**17** was isolated in good yield and was deprotected to give (+)-**2** which displayed identical ^1H and ^{13}C NMR spectra to those of the sample prepared according to Scheme 1. The azepane (−)-**2** was synthesized by the same method from (+)-**15**.



Scheme 3. (a) $NaI)O_4/SiO_2$, CH_2Cl_2; (b) $NaBH(OAc)_3$, $BnNH_2$, CH_2Cl_2, (a, b 86%); (c) H_2, $Pd(OH)_2/C$, MeOH/AcOH (trace) (92%).

Although short and efficient, this synthesis of (−)- and/or (+)-**2** requires the resolution of *myo*-inositol. In our hands the literature procedure, conducted via the camphor acetal,[26,27] required the use of both crystallization and chromatography to afford homochiral material.

In vitro inhibition profiles of the tetrahydroxyazepanes (−)-, (+)-**1** and (−)-, (+)-**2** were determined against eight enzymes, α-L-naringinase being a 6-deoxy-α-L-mannosidase (Table 1). Much the most active, but least selective, isomer, the L-*ido*-compound (+)-**2**, gave mainly analogous results to those already reported for this inhibitor with α- and β-glucosidase, α-mannosidase, α- and β-galactosidase and α-fucosidase.[8,12] However, Wong et al. found that it also inhibited β-D-*N*-acetylglucosaminidase[8] which is contrary to the result given in Table 1. In our hands azepane (+)-**2** showed no inhibition of this enzyme (lit.[8] $K_i = 22.7$ μM). Potent inhibitors of hexosaminidase most often but not always,[28] feature an acetamido-functional group, so it was not surprising that (+)-**2** did not inhibit β-*N*-acetylglucosaminidase. As a positive control, the known hexosaminidase inhibitor 2-acetamido-1,2-dideoxynojirimycin[29] was assayed against this enzyme and, under the assay conditions used >99% inhibition was observed, thus confirming the integrity of the inhibition assay. The enantiomer (−)-**2** was much less potent, but showed some activity against all but one of the enzymes tested. On the other hand, the D- and L-*manno*-enantiomers (−)- and (+)-**1** were selective towards α-fucosidase and α-galactosidase, respectively, while also inhibiting β-galactosidase. (−)-**1** Showed only minor inhibition (28% at 1.67 mM, lit.[8] $K_i = 4.6$ μM) against β-D-*N*-acetylglucosaminidase.

Table 1. Glycosidase inhibition by tetrahydroxyazepanes[a]

Glycosidase	Inhibitor			
	(+)-**2**	(−)-**2**	(−)-**1**	(+)-**1**
α-D-Glucosidase (from *Bacillius stearothermophilus*)	95 $IC_{50} = 6$ μM	20	25	38
β-D-Glucosidase (from sweet almonds)	98 $IC_{50} = 10$ μM	20	N.I.	30
β-D-*N*-Acetylglucosaminidase (from jack beans)	N.I.[b]	N. I.	28	5
α-D-Mannosidase (from jack beans)	99 $IC_{50} = 17$ μM	85 $IC_{50} = 165$ μM	69 $IC_{50} = 695$ μM	N.I.
α-L-Naringinase (from *Penicillium decumbens*)	84	81	5	20
α-D-Galactosidase (from green coffee beans)	39	34	42	98 $IC_{50} = 4$ μM $K_i = 4.9 \pm 1.5$ μM[c]
β-D-Galactosidase (from *A. oryzae*)	100 $IC_{50} = 20$ μM	79 $IC_{50} = 335$ μM	94 $IC_{50} = 98$ μM	94 $IC_{50} = 95$ μM
α-L-Fucosidase (from bovine kidney)	78	15	97 $IC_{50} = 9$ μM	39

[a] Percent inhibition at inhibitor concentration of 1.67 mM.
[b] N.I., no inhibition.
[c] The K_i was also determined using the computer program *Grafit* (purchased from Erithacus Software) and gave $K_i = 3.0 \pm 0.5$ μM.

As might be expected, in some cases there is strong correlation between the configurations of the inhibitors and those of the substrates of the corresponding inhibited enzymes, but the same does not apply in all instances. For example, there is complete correlation between the configuration of (+)-**1** and that at C-1–C-4 of the α-D-galactopyranosides and, likewise, (−)-**1** and the α-L-fucopyranosides are stereochemically analogous. However, in the case of the D-*ido*-isomer (−)-**2** correlation with α-D-mannosides occurs at two contiguous chiral centers only and with the β-galactosides at three contiguous chiral centres and, surprisingly, since this isomer and β-glucosides have the same configuration, there is only mild inhibition of the β-glucosidase. The least selective but potent inhibitor, (+)-**2**, has a contiguous *xylo*-triol that also occurs in the glucosides and β-galactosides and there is good inhibition of the respective enzymes in all cases, but for the α-mannosides, only two centers are common to the glycosides and the inhibitor (+)-**2**, yet there is good inhibition.

3. Conclusion

Concise syntheses, from inositols, of the tetrahydroxyazepanes (−)-, (+)-**1** and (−)-, (+)-**2** have been developed. The L-*manno*-compound (+)-**1** is a novel selective inhibitor of α-D-galactosidase, while the (−)-**1** enantiomer inhibits α-L-fucosidase selectively. Less selectivity is shown by the *ido*-isomers (**2**), but the (+)-isomer is active against several enzymes. There is some correlation between the configurations of the inhibitors and those of the substrates of the enzymes inhibited. Surprisingly, however, (−)-**2** only inhibits β-glucosidase very poorly. Some of the apparent anomalies may be explained by the extra flexibility of tetrahydroxyazepanes[11] as compared with pyranoses.

4. Experimental

D-*chiro*-Inositol and L-*chiro*-inositol were prepared by demethylation[30] of pinitol (New Zealand Pharmceuticals Ltd) and quebrachitol (Rubber Research Institute of Malaysia), respectively. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-300 spectrometer at 300 and 75 MHz, respectively, using deuteriochloroform as solvent (unless otherwise stated) and tetramethylsilane as internal standard unless otherwise indicated. In the ^{13}C spectra the numbers of attached protons were determined by DEPT experiments. Mass spectra were recorded at the Mass Spectrometry Unit, Hort. Research, Palmerston North, New Zealand on a VG70-250S double focusing, magnetic sector mass spectrometer under chemical ionization conditions using isobutene or ammonia as the ionizing gas, or under high-resolution FAB conditions in a glycerol or nitrobenzyl alcohol matrix. Microanalyses were carried out by the Campbell Microanalytical Laboratory, University of Otago. Melting points were determined using a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a 1 dm path length cell. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick Merck 60 F254 silica gel plates. Visualization was by UV exposure, or by thermal development after spraying with basic potassium permanganate or ethanolic phosphomolybdic acid. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) under air pressure.

4.1. (2′*R*,3′*R*)-1D-1,2-Anhydro-3,4:5,6-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(−)-7]

Diethyl azodicarboxylate (3.65 mL, 23.2 mmol) was added dropwise over 3–4 min to a stirred solution of diol (−)-**6** (9.18 g, 22.5 mmol) and triphenylphosphine (6.00 g, 22.9 mmol) in anhydrous THF (75 mL) cooled to 0 °C under argon. After 90 min stirring at 0 C the reaction mixture was concentrated in vacuo to 10% of the original volume and diluted with ether (200 mL). The ether phase was washed with HCl (120 mL, 2M) and the aqueous phase was extracted with ether (2×150 mL). The combined ethereal extracts were washed with aqueous $NaHCO_3$ (200 mL, saturated) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the product was purified by flash chromatography. Elution with EtOAc/light petroleum (1:3) afforded (−)-**7** as a white solid (5.94 g, 15.2 mmol, 68%); mp 73–75 °C; $[\alpha]_D^{20}$ −232 (*c* 0.92, $CDCl_3$); ^{1}H NMR δ 4.10–4.05 (1H, m), 3.95–3.89 (1H, m), 3.69–3.58 (2H, m), 3.30–3.25 (1H, m), 3.29 (3H, s), 3.28 (3H, s), 3.26 (3H, s), 3.24 (3H, s), 3.13 (1H, d, *J* 3.8), 1.34 (3H, s), 1.32 (3H, s), 1.29 (3H, s), 1.28 (3H, s); ^{13}C NMR101.1 (C), 100.8 (C), 100.0 (C), 99.8 (C), 70.8 (CH), 69.0 (CH), 68.6 (CH), 64.6 (CH), 54.4 (CH), 53.2 (CH), 48.5 (CH_3), 48.4 (CH_3), 48.2 (CH_3), 18.0(3) (CH_3), 17.9(7) (CH_3); *m*/*z* (FAB, DCM/NBA) 389 [$(M-H)^+$, 2%], 359 (100), 327 (10), 209 (5); HRMS *m*/*z* calcd for $C_{18}H_{30}O_9$ $(M)^+$ 390.1890, found 390.1898.

4.2. (2′*R*,3′*R*)-1D-1-Deoxy-1-iodo-2,3:4,5-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*chiro*-inositol [(−)-8]

Aluminum trichloride (2.61 g, 19.6 mmol) was added in portions to a stirred solution of the epoxide (−)-**7** (5.94 g, 15.2 mmol) and sodium iodide (6.10 g, 40.7 mmol) in anhydrous MeCN (120 mL) at 0 °C under argon. After 20 min stirring at 0 °C the reaction mixture was concentrated in vacuo and the residue was taken up in ether (200 mL). The ether phase was washed with water (150 mL) and the aqueous phase extracted with further ether (2×150 mL). The combined ethereal extracts were washed with aqueous $NaHCO_3$ (200 mL, saturated) then with aqueous $Na_2S_2O_3$ (2×150 mL, saturated) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the residue purified by flash chromatography. Elution with EtOAc/light petroleum (1:4–1:1.5) afforded iodo alcohol (−)-**8** as a white solid (7.48 g, 14.4 mmol, 95%). Crystallization from EtOH–H_2O gave white prisms; mp 178–179 °C; $[\alpha]_D^{20}$ −161 (*c* 0.90, $CHCl_3$); ^{1}H NMR δ 4.39 (1H, dd, *J* = 9.8, 2.8 Hz), 4.31 (1H, dd, *J* = 4.0, 3.1 Hz), 4.22 (1H, bt, *J* = 2.7 Hz), 4.05 (1H, t, *J* = 10.0 Hz), 3.94 (1H, t, *J* = 9.6 Hz), 3.34 (1H, dd, *J* = 9.2, 4.2 Hz), 3.28 (3H, s), 3.28 (3H, s), 3.26 (3H, s), 3.24 (3H, s), 2.85 (1H, bs), 1.31 (3H, s), 1.30 (3H, s), 1.28 (3H, s), 1.26 (3H, s); ^{13}C NMR δ 100.8 (C),

100.6 (C), 99.4 (C), 99.1 (C), 74.1 (CH), 69.4 (CH), 68.4 (CH), 67.1 (CH), 66.1 (CH), 48.5 (CH_3), 48.4 (CH_3), 48.3 (CH_3), 29.3 (CH), 18.1 (CH_3), 18.0 (CH_3); *m/z* (FAB, NBA) 519 [$(M+H)^+$, 1%], 517 (1), 503 (2), 487 (20), 101 (100); HRMS *m/z* calcd for $C_{18}H_{30}IO_9$ $(M\text{-}H)^+$ 517.0935, found 517.0943. Anal. calcd for $C_{18}H_{31}IO_9$: C, 41.71; H, 6.03; I, 24.48. Found: C, 41.8; H, 6.0; I, 24.5.

4.3. (2′*R*,3′*R*)-1D-1-Deoxy-1-iodo-6-*O*-methanesulfonyl-2,3:4,5-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*chiro*-inositol [(−)-9]

Triethylamine (15.0 mL, 108 mmol) was added dropwise to a stirred solution of iodo alcohol (−)-**8** (5.66 g, 10.9 mmol) and methanesulphonyl chloride (2.53 mL, 32.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C under argon. The ice bath was removed and the reaction mixture was stirred at rt for 14 h. It was diluted with CH_2Cl_2 (120 mL) and washed with HCl (100 mL, 2M), and the aqueous phase was extracted with further CH_2Cl_2 (100 mL). The combined organic extract was washed with brine (150 mL) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo and the product was purified by flash chromatography. Elution with EtOAc/light petroleum (1:9–1:1) afforded alkene (−)-**10** as a colourless oil (469 mg, 1.25 mmol, 11%) followed by the iodo mesylate (−)-**9** as a colourless oil (3.70 g, 6.20 mmol, 57%), $[\alpha]_D^{25}$ −153 (*c* 0.50, $CHCl_3$); ^1H NMR δ 5.03 (1H, t, *J* = 2.9 Hz), 4.61 (1H, dd, *J* = 9.9, 2.7 Hz), 4.35 (1H, dd, *J* = 4.2, 3.3 Hz), 4.03 (1H, t, *J* = 9.9 Hz), 3.92 (1H, t, *J* = 9.4 Hz), 3.29 (3H, s), 3.28 (3H, s), 3.26 (3H, s), 3.24 (4H, bs+), 3.14 (3H, s), 1.31 (3H, s), 1.29 (3H, s), 1.28 (3H, s), 1.27 (3H, s); ^{13}C NMR δ 100.8 (C), 99.3 (C), 82.4 (CH), 69.1 (CH), 66.9 (CH), 66.4 (CH), 65.9 (CH), 48.6 (CH_3), 48.5 (CH_3), 39.4 (CH_3), 25.7 (CHI), 18.0 (CH_3), 17.9 (CH_3); *m/z* (FAB, NBA) 595 [$(M\text{-}H)^+$, 5%], 581 (10), 575 (5), 565 (30), 173 (20), 115 (60), 101 (100); HRMS *m/z* calcd for $C_{19}H_{33}IO_{11}S$ $(M)^+$ 596.0788, found 596.0802.

4.4. (2*S*,3*R*,4*R*,5*S*,2′*R*,3′*R*) - 2,3:4,5 - Bis - *O* - (2′,3′ - dimethoxybutane-2′,3′-dioxy)-cyclohexene [(−)-10]

Anhydrous DMF (20 mL) was cannulated onto a mixture of the iodo mesylate (−)-**9** (3.70 g, 6.20 mmol) and zinc dust (1.31 g, 20.0 mmol) under argon. The suspension was heated with stirring to 80 °C and acetic acid (10 mL) was injected. After being stirred at this temperature for 40 min the reaction mixture was cooled to rt and filtered through Celite which was washed with ether (3×100 mL) and the combined filtrate and washings were concentrated in vacuo. The residue was purified by flash chromatography and elution with EtOAc/light petroleum (1:9–1:3) afforded the alkene (−)-**10** as a thick gum (2.13 g, 5.70 mmol, 92%), $[\alpha]_D^{25}$ −164 (*c* 0.76, $CHCl_3$); ^1H NMR δ 5.56 (2H, bs), 4.45–4.40 (2H, m), 3.95–3.90 (2H, m), 3.29 (6H, s), 3.24 (6H, s), 1.31 (12H, bs); ^{13}C NMR δ 127.6 (CH), 100.9 (C), 100.2 (C), 70.5 (CH), 68.8 (CH), 48.5 (CH_3), 48.1 (CH_3), 18.2 (CH_3), 18.1 (CH_3); *m/z* (FAB, NBA/DCM) 373 [$(M\text{-}H)^+$, 1%], 343 (5), 211 (5), 116 (20), 101 (100); HRMS *m/z* calcd for $C_{18}H_{29}O_8$ $(M-H)^+$ 373.1862, found 373.1844. Anal. calcd for $C_{18}H_{30}O_8$: C, 57.74; H, 8.08. Found: C, 57.6; H, 7.8.

4.5. (2′*R*,3′*R*)-1D-3,4:5,6-Bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(−)-11]

Alkene (−)-**10** (138 mg, 0.369 mmol) in EtOAc (3 mL) was added to a stirred solution of $NaIO_4$ (88.0 mg, 0.411 mmol) in H_2O (1 mL) and MeCN (3 mL). To this mixture was added $RuCl_3$ (10.0 mg, 48.2 μmol). The reaction mixture was stirred for 10 min and aqueous $Na_2S_2O_3$ (10 mL, saturated) was added and the stirring was continued for a further 15 min. The reaction mixture was extracted with ether (3×30 mL) and the combined ethereal extracts were dried ($MgSO_4$). After filtration, the solvent was removed in vacuo to give diol (−)-**11** as a syrup (147 mg, 0.360 mmol, 98%), $[\alpha]_D^{22}$ −246 (*c* 0.52, $CHCl_3$); ^1H NMR δ 4.11 (1H, t, *J* = 2.8 Hz), 4.06 (1H, t, *J* = 10.0 Hz), 3.92 (1H, t, *J* = 9.9 Hz), 3.65 (1H, dd, *J* = 9.7, 2.9 Hz), 3.61 (1H, t, *J* = 9.9 Hz), 3.52 (1H, dd, *J* = 9.9, 2.6 Hz), 3.28 (3H, s), 3.27 (6H, s), 3.23 (3H, s), 2.68 (1H, bs), 2.46 (1H, bs), 1.33 (3H, s), 1.32 (3H, s), 1.30 (3H, s), 1.28 (3H, s); ^{13}C NMR δ 100.6 (C), 100.0 (C), 99.5 (C), 99.3 (C), 70.7 (CH), 70.4 (CH), 70.3 (CH), 69.4 (CH), 68.3 (CH), 66.0 (CH), 48.4 (CH_3), 48.3 (CH_3), 48.2 (CH_3), 18.1 (CH_3), 18.0 (CH_3); *m/z* (EI) 377 [$(M\text{-}OCH_3)^+$, 5%], 112 (100), 101 (80); HRMS (EI) *m/z* calcd for $C_{17}H_{29}O_{10}$ $(M\text{-}Me)^+$ 393.1761, found 393.1768.

4.6. (2′*R*,3′*R*)-2,3:4,5-Bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*ido*-hexodialdose [L-12]

A solution of the diol (−)-**11** (147 mg, 0.360 mmol) in CH_2Cl_2 (5 mL) was added to a stirred suspension of $NaIO_4$ (0.30 g, 1.6 mmol) adsorbed on silica gel (1.15g).[18] The suspension was stirred at rt for 14 h and filtered through a pad of silica. The solids were washed with EtOAc (25 mL) and the solvents removed in vacuo to give essentially pure syrupy dialdehyde L-**12** (140 mg, 0.341 mmol, 95%). A sample of the dialdehyde was dried by heating in refluxing C_6D_6 under argon in a Dean Stark apparatus for 20 min. ^1H NMR δ (C_6D_6) 9.62 (2H, d, *J* = 1.5 Hz), 4.78 (2H, d, *J* = 9.7 Hz), 4.57 (2H, d, *J* = 9.7 Hz), 3.32 (6H, s), 3.11 (6H, s), 1.40 (6H, s), 1.34 (6H, s); ^{13}C NMR δ (C_6D_6) 198.4 (CH), 98.0 (C), 97.9 (C), 70.7 (CH), 63.8 (CH), 47.4 (CH_3), 46.6 (CH_3), 16.5 (CH_3), 16.4 (CH_3); *m/z* (FAB, NBA/DCM) 375 [$(M-OCH_3)^+$, 5%], 343 (8), 243 (5), 116 (30), 101 (100), 73 (20). HRMS *m/z* calcd for $C_{18}H_{31}O_{10}$ $(M+H)^+$ 407.1917, found 407.1934.

4.7. (3*S*,4*R*,5*R*,6*S*,2′*R*,3′*R*)-*N*-(Diphenyl)methyl-3,4:5,6-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-dioxy)-azepane [(−)-13]

Acetic acid (40 μL, 0.67 mmol) was injected into a stirred mixture of the dialdehyde (140 mg, 0.329 mmol), sodium cyanoborohydride (60 mg, 0.96 mmol) and oven dried 3 Å molecular sieves (0.60 g) in MeOH (25 mL) at −78 °C under argon. (Diphenylmethyl)amine (50 μL, 0.29 mmol) was added dropwise to over 10 min. The cold bath was removed and the reaction mixture stirred at rt for 17 h, then filtered through Celite and the Celite was washed with EtOAc (2×50 mL). The combined filtrate and washings were taken to dryness in vacuo and the remaining residue was taken up in diethyl ether (100

mL) and washed with aqueous $NaHCO_3$ (80 mL, saturated). The aqueous phase was extracted with diethyl ether (2×50 mL) and the combined organic phases were washed with brine (100 mL) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo to give the crude product (175 mg) which was purified by flash chromatography. Elution with CH_2Cl_2 then EtOAc in CH_2Cl_2 (1:9) afforded the azepane derivative (−)-**13** as a colourless oil (110 mg, 0.197 mmol, 60%), $[\alpha]_D^{19}$ −187 (*c* 0.48, $CHCl_3$); ^1H NMR δ 7.38–7.34 (4H, m), 7.30–7.20 (4H, m), 7.19–7.12 (2H, m), 4.66 (1H, s), 3.88–3.80 (2H, m), 3.72–3.66 (2H, m), 3.26 (6H, s), 3.21 (6H, s), 2.82 (2H, dd, *J* = 13.5, 2.0 Hz), 2.62 (2H, dd, *J* = 13.5, 9.5 Hz), 1.25 (6H, s), 1.18 (6H, s); ^{13}C NMR δ 142.9 (C), 142.4 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.4(5) (CH), 127.5 (CH), 99.5 (C), 98.6 (C), 75.5 (CH), 73.6 (CH), 66.0 (CH), 53.1 (CH_2), 48.4 (CH_3), 48.1 (CH_3), 17.9 (CH_3); *m/z* (FAB, NBA/DCM) 556 [$(M-H)^+$, 10%], 167 (100), 116 (15), 101 (10). HRMS *m/z* calcd for $C_{31}H_{43}NO_8$ $(M)^+$ 557.2987, found 557.2993.

4.8. (3*S*,4*R*,5*R*,6*S*) - *N* - Diphenylmethyl - 3,4,5,6 - tetrahydroxyazepane [(+)-14]

Water (0.1 mL) was added dropwise to a stirred solution of the azepane derivative (−)-**13** (110 mg, 0.197 mmol) in TFA (2.5 mL). After the solution had been stirred for 12 h at rt the solvents were removed in vacuo and the residue was taken up in ether (50 mL) and aqueous NaOH (30 mL, 0.5 M). The aqueous phase was extracted with further ether (2×30 mL) and the combined ethereal solutions were dried ($MgSO_4$). After filtration, the solvent was removed in vacuo. The product was purified by flash chromatography. Elution with EtOAc then MeOH–EtOAc (1:40) afforded the *N*-protected tetrahydroxyazepane (+)-**14** as a white solid (49.0 mg, 0.149 mmol, 76%), mp 91–92 °C; $[\alpha]_D^{22}$ +55 (*c* 0.22, CD_3OD); ^1H NMR (CD_3OD) δ 7.39–7.10 (10H, m), 4.64 (1H, s), 3.58 (4H, bs), 2.91–2.78 (2H, m), 2.59–2.47 (2H, m); ^{13}C NMR δ (CD_3OD) 142.5 (C), 142.4 (C), 129.0 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 76.3 (CH), 75.8 (CH), 73.2 (CH), 57.9 (CH_2); *m/z* (FAB, glycerol/H_2O,) 330 $[M+H]^+$, 30%], 167 (100). HRMS *m/z* calcd for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1705, found 330.1735. Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.3; H, 7.0; N, 4.2.

4.9. (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydroxyazepane [(+)-2]

Palladium hydroxide on carbon (20% Pd, 32 mg) was added to a stirred solution of the *N*-protected tetrahydroxyazepane (+)-**14** (43 mg, 0.13 mmol) in MeOH (5 mL). The reaction atmosphere was changed to hydrogen and the mixture was stirred for 14 h. The hydrogen was removed and the suspension was filtered through Celite. The Celite was washed with MeOH and then water, the combined filtrate and washings were concentrated in vacuo and the residue was partitioned between H_2O (10 mL) and light petroleum (10 mL). The aqueous phase was washed with a further portion of light petroleum (10 mL), separated and centrifuged (1500 rpm 15 min). The supernatant was then concentrated in vacuo to give (+)-**2** as a low melting yellow solid (20 mg, 0.12 mmol, 92%), $[\alpha]_D^{20}$ +6.3 (*c* 0.40, H_2O, HCl salt); ^1H NMR δ (D_2O/DCl) 3.99–3.90 (2H, m), 3.59–3.54 (2H, m), 3.23 (2H, dd, *J* = 13.8, 2.1 Hz), 3.08 (2H, dd, *J* = 13.8, 8.1 Hz); ^{13}C NMR δ (D_2O/DCl) 76.9 (CH), 67.8 (CH), 47.1 (CH_2); *m/z* (FAB, glycerol/H_2O) 164 $[(M+H)^+$, 100%], 115 (30). HRMS *m/z* calcd for $C_6H_{14}NO_4$ $(M+H)^+$ 164.0923, found 164.0940.

The following compounds were made from 1L-*chiro*-inositol by the methods described above for their enantiomers, NMR data obtained was essentially identical to that reported for their enantiomers.

4.10. (2′*S*,3′*S*)-1L-2,3:4,5-Bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*chiro*-inositol [(+)-6][16a]

Pale brown foam, $[\alpha]_D^{20}$ +184 (*c* 1.50, $CDCl_3$); *m/z* (FAB, DCM/NBA) 409 $[(M+H)^+$, 1%], 407 (2), 393 (2), 377 (25), 101 (100); HRMS *m/z* calcd for $C_{18}H_{31}O_{10}$ $(M-H)^+$ 407.1917, found 407.1886.

4.11. (2′*S*,3′*S*)-1L-1,2-Anhydro-3,4:5,6-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(+)-7]

White solid, mp 74–75 °C; $[\alpha]_D^{20}$ +221 (*c* 1.41, $CDCl_3$); HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{18}H_{29}O_9$ $(M-H)^+$ 389.1812, found 389.1815.

4.12. (2′*S*,3′*S*)-1L-6-Deoxy-6-iodo-2,3:4,5-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*chiro*-inositol [(+)-8]

$[\alpha]_D^{21}$ +178 (*c* 2.22, $CHCl_3$); *m/z* (FAB, NBA/MeOH) 517 $[(M-H)^+$, 1%], 503 (2), 487 (30), 337 (5), 211 (7), 115 (30), 101 (100), 73 (25); HRMS *m/z* calcd for $C_{18}H_{31}IO_9$ $(M)^+$ 518.1013, found 518.0968.

4.13. (2*R*,3*S*,4*S*,5*R*,2′*S*,3′*S*) - 2,3:4,5 - Bis - *O* - (2′,3′ - dimethoxybutane-2′,3′-dioxy)-cyclohexene [(+)-10]

Pyridine (0.820 mL, 10.1 mmol) was added dropwise to a stirred solution of (+)-**8** (2.02 g, 3.90 mmol) and triflic anhydride (0.920 mL, 5.47 mmol) in anhydrous DMF (50 mL) at 0 °C under argon. The cold bath was removed and after the solution had been stirred at rt for 90 min Zn-dust (420 mg, 6.32 mmol) and acetic acid (6 mL) were added and the stirring was continued for 10 h. After the addition of aqueous $NaHCO_3$ (120 mL, saturated) the reaction mixture was extracted with ether (3×100 mL) and the combined ethereal extracts were washed with H_2O (5×80 mL). After being dried ($MgSO_4$) and filtered, the solvent was removed in vacuo to give essentially pure (+)-**10** as a thick gum (1.39 g, 3.72 mmol, 95%), $[\alpha]_D^{20}$ +175 (*c* 1.50, $CHCl_3$); *m/z* (FAB, NBA/MeOH) 373 $[(M-H)^+$, 1%], 343 (10), 211 (4), 116 (20), 101 (100), 78 (25); HRMS *m/z* calcd for $C_{18}H_{29}O_8$ $(M-H)^+$ 373.1862, found 373.1848.

4.14. (2′*S*,3′*S*)-1L-3,4:5,6-Bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(+)-11]

$[\alpha]_D^{22}$ +232 (*c* 0.64, $CHCl_3$); *m/z* (FAB, NBA/MeOH) 431 $[(M+Na)^+$, 3%), 407 (1), 393 (3), 377 (60), 345 (5),

313 (8), 116 (20), 101 (100), 73 (20); HRMS *m/z* calcd for $C_{18}H_{31}O_{10}$ $(M-H)^+$ 407.1917, found 407.1897.

4.15. (2′*S*,3′*S*)-2,3:4,5-Bis-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-D-*ido*-hexodialdose [D-12]

Syrup, *m/z* (FAB, NBA/MeOH) 375 [$(M-OCH_3)^+$, 5%)], 343 (7), 243 (5), 116 (20), 101 (100), 73 (20); HRMS *m/z* calcd for $C_{18}H_{31}O_{10}$ $(M+H)^+$ 407.1917, found 407.1931.

4.16. (3*R*,4*S*,5*S*,6*R*,2′*S*,3′*S*)-*N*-Diphenylmethyl-3,4:5,6-bis-*O*-(2′,3′-dimethoxybutane-2′,3′-dioxy)-azepane [(+)-13]

Syrup, $[\alpha]_D^{22}$ +191 (*c* 0.84, $CHCl_3$); *m/z* (FAB, NBA/MeOH) 556 [$(M-H)^+$, 5%], 526 (3), 167 (100), 116 (10), 101 (5); HRMS *m/z* calcd for $C_{31}H_{43}NO_8$ $(M)^+$ 557.2987, found 557.2995.

4.17. (3*R*,4*S*,5*S*,6*R*)-*N*-Diphenylmethyl-3,4,5,6-tetrahydroxyazepane [(−)-14]

White solid; mp 89–90 °C; $[\alpha]_D^{20}$ −62 (*c* 0.20, CD_3OD); *m/z* (FAB, glycerol–H_2O) 330 [$(M+H)^+$, 60%], 167 (100); HRMS *m/z* calcd for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1705, found 330.1699.

4.18. (3*R*,4*S*,5*S*,6*R*)-3,4,5,6-Tetrahydroxyazepane [(−)-2]

Low melting yellow solid, $[\alpha]_D^{20}$ −6.5 (*c* 0.40, H_2O, HCl salt); *m/z* (FAB, glycerol–H_2O) 164 [$(M+H)^+$, 100%]; HRMS *m/z* calcd for $C_6H_{14}NO_4$ $(M+H)^+$ 164.0923, found 164.0917.

4.19. (3*S*,4*R*,5*R*,6*S*)-*N*-Benzyl-3,4,5,6-tetra-*O*-benzyl-azepane [(+)-17]

A solution of the diol (−)-**15**[25] (100 mg, 0.185 mmol) in CH_2Cl_2 (2.5 mL) was added to a stirred suspension of $NaIO_4$ (0.318 g, 1.66 mmol) absorbed on silica (1.18 g) in CH_2Cl_2 (2.5 mL). The suspension was stirred at rt for 3.5 h, filtered and the residue was washed with EtOAc (10 mL) and then with CH_2Cl_2 (10 mL). The solvents were removed in vacuo to give dialdehyde (+)-**16** (99 mg, 0.18 mmol, 99%). Triacetoxyborohydride (114 mg, 0.538 mmol) was added to a stirred solution of this dialdehyde and benzylamine (24.0 μL, 0.216 mmol) in CH_2ClCH_2Cl (5 mL) under argon. After stirring the mixture at rt for 18 h $NaHCO_3$ (500 mg) was added and the reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and H_2O (30 mL). The aqueous phase was re-extracted with EtOAc (50 mL) and the combined organic extracts were washed with aqueous $NaHCO_3$ (30 mL, saturated) and brine (30 mL). After drying of the solution ($MgSO_4$) and filtration, the filtrate was taken to dryness in vacuo to give the crude product which was purified by flash chromatography. Elution with EtOAc/light petroleum (1:20–1:9) afforded (+)-**17** [113 mg, 0.184 mmol, 99% from (−)-**15**] as a clear oil; $[\alpha]_D^{22}$ +15.3 (*c* 2.22, $CHCl_3$); ^{1}H NMR δ 7.44–7.07 (20H, m), 4.60 (4H, q, *J* = 11.4, 5.1 Hz), 4.45 (4H, q, *J* = 12.0, 12.6 Hz) 3.76 (4H, s) 3.61 (2H, s) 2.77–2.63 (4H, m); ^{13}C NMR δ 139.5 (C), 139.2 (C), 139.1 (C), 129.4 (CH), 128.6 (CH), 128.0 (2 lines, CH), 127.7 (CH), 127.4 (CH), 84.1 (CH), 80.2 (CH), 74.2 (CH), 72.3 (CH), 63.2 (CH), 54.8 (CH); *m/z* (FAB, NBA/DCM) 614 [$(M+H)^+$, 100%], 506 (10) 391 (9) 149(13) 91 (60). HRMS *m/z* calcd for $C_{41}H_{44}NO_4$ $(M+H)^+$ 614.3270, found 614.3290.

4.20. 2,3,4,5-Tetra-*O*-benzyl-L-*ido*-hexodialdose [(−)-16]

$[\alpha]_D^{22}$ −15.7 (*c* = 0.64, $CHCl_3$); ^{1}H NMR δ 9.66 (2H, s), 7.33–7.21. (20H, m), 4.75 (2H, d, *J* = 12 Hz) 4.56 (2H, d *J* = 12 Hz), 4.38 (4H, d, *J* = 12 Hz) 4.03 (2H, d, *J* = 6 Hz) 3.69 (2H, d, *J* = 6 Hz); ^{13}C NMR δ 200.4 (2×C=O) 137.6 (C) 137.5 (C) 129.0 (CH) 128.9 (CH); 128.9 (CH), 128.5 (CH), 128.5 (CH),80.8 (CH), 78.8 (CH),74.3 (CH) 73.3 (CH); *m/z* (FAB, NBA/DCM) 539 $[M+H]^+$, 1%], 181 (21) 91 (100); HRMS *m/z* calcd for $C_{34}H_{35}O_6$ $(M+H)^+$ 539.2434, found 539.2419.

4.21. (3*R*,4*S*,5*S*,6*R*)-*N*-Benzyl-3,4,5,6-tetra-*O*-benzyl-azepane [(−)-17]

$[\alpha]_D^{22}$ −15.9 (*c* 3.3, $CDCl_3$), *m/z* (FAB, NBA/DCM) 614 [$(M+H)^+$, 100%], 506 (9) 391 (19) 149 (59) 55 (83); HRMS *m/z* calcd for $C_{41}H_{44}NO_4$ $(M+H)^+$ 614.3270, found 614.3252.

4.22. (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydroxyazepane [(+)-2]

$Pd(OH)_2$ on carbon (650 mg) was added to a solution of (+)-**17** (113 mg, 0.184 mmol) and acetic acid (5 μL, 0.08 mmol) in MeOH (7 mL). Hydrogen was introduced (to 200 psi) and the mixture was stirred for 72 h. After removal of the hydrogen the mixture was filtered through Celite. The pad was washed with MeOH (30 mL) and the solvent and washings were concentrated in vacuo to give (+)-**2** (17 mg, 0.104 mmol, 57%); $[\alpha]_D^{22}$ +9.8 (*c* 0.65, D_2O); *m/z* (FAB, glycerol–MeOH) 164 [$(M+H)^+$, 15%], 146 (12) 115 (16); HRMS *m/z* calcd for $C_6H_{14}NO_4$ $(M+H)^+$ 164.0902, found 164.0923.

4.23. Glycosidase assay conditions

All inhibition assays were performed in 0.1 M HEPES buffer at 37 °C and pH 6.8. The amount of enzyme used varied from 0.01 to 0.05 units in a total volume of 300 μL. The concentration of the *p*-nitrophenyl glycosides used as substrates was 500 μM for % inhibition and IC_{50} determinations. Values in Table 1 were determined at an inhibitor concentration of 1.67 mM. The optical absorbance was measured at 410 nm after a 5-min incubation time. Assays were quenched by the addition of sodium borate buffer at pH 9.8 (100 μL). For K_i determinations, substrate concentrations ranged from 0.25 to 6.00 mM and inhibitor concentrations ranged from 2.1 to 33 μM.

Acknowledgements

The authors thank Dr Herbert Wong for an excellent NMR service, Dr J. B. Hart and Dr J. A. Gerrard for help with the glycosidase assays, Prof George Fleet for insightful ideas and the Foundation for Research, Science

and Technology for financial support (Science and Technology Post-Doctoral Fellowship, contract #C08821 to G.F.P. and Public Good Science Fund, contract #C08811-D, to A.F.). Prof Robin Ferrier assisted with the preparation of the manuscript.

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