# Short practical synthesis of (3*R*,4*R*,5*R*,6*R*)-tetrahydroxyazepane and (3*S*,4*S*,5*S*,6*S*)-tetrahydroxyazepane from D- and L-*chiro*-inositol, respectively

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The polyhydroxylated azepanes (3*R*,4*R*,5*R*,6*R*)-tetrahydroxyazepane (−)-**1** and (3*S*,4*S*,5*S*,6*S*)-tetrahydroxyazepane (+)-**1** are synthesised from D-and L-*chiro*-inositol, respectively. Key transformations in the reaction sequence include a glycol-fission reaction with sodium metaperiodate supported on silica gel and the double reductive amination of a *manno*-1,6-dialdehyde derivative. This work represents the first synthesis of tetrahydroxyazepanes from inositols.

## Introduction

The biological properties of the various azasugars are well documented. Their main application has been associated with their ability to inhibit glycosidase enzymes.[1,2] Much work has been devoted to the preparation and subsequent evaluation of five- and six-membered azasugars,[3] however only a few reports have appeared[4–10] on the synthesis of the seven-membered analogues despite their inhibitory potential.[6,9,10] Of particular interest, (−)-**1** has been shown[6] to be a potent β-*N*-acetylglucosaminidase inhibitor. To date, the synthetic preparations of tetrahydroxyazepanes generally utilise sugars as starting materials. Although sometimes efficient, this approach does not generally allow access to the enantiomeric series and often results in the formation of piperidine derivatives that need to be separated.[9,10] In setting up glycosidase-inhibitory assays we considered access to the enantiomers important in assessing the specificity of any glycosidase-active site. The synthetic work presented here utilises D- and L-*chiro*-inositol as readily available and cheap starting materials.

Double reductive amination of dicarbonyl sugars is an established method for the preparation of aminosugars (Fig. 1).[11–13] Retrosynthetically, this methodology would require the *manno*-1,6-dialdehyde **2** which, in turn, could be derived from diol **3** by glycol oxidative fission. We now report the concise syntheses of tetrahydroxyazepanes (−)-**1** and (+)-**1** from *chiro*-inositol.

## Results and discussion

Bis-acetonide **4**[14] was obtained from D-*chiro*-inositol *via* the selective hydrolysis of the tris-acetonide.[15] Bis-acetonide **4** was oxidatively cleaved with sodium metaperiodate supported on silica gel[16] to give dialdehyde (−)-**5**[17] (Scheme 1). The dialdehyde could be filtered through silica and used directly for the next step or crystallised from ethyl acetate. However, on storage it was noted that the material, at least in part, formed a hydrate

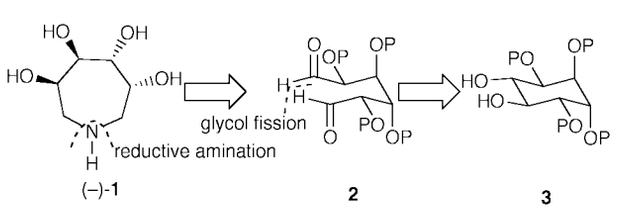
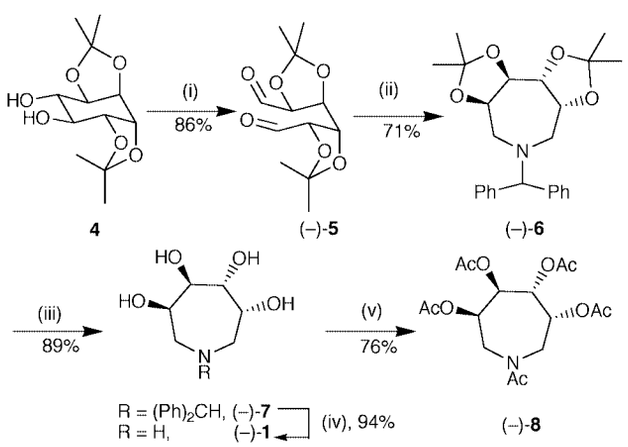



**Fig. 1** Retrosynthetic analysis of (−)-**1** *via* reductive amination and glycol fission.




**Scheme 1** *Reagents and conditions*: (i), $NaIO_4$-activated silica, $CH_2Cl_2$; (ii), $NaCNBH_3$, $(Ph)_2CHNH_2$, AcOH (2 equiv.), 3 Å molecular sieves, MeOH, −78 °C to RT; (iii), c. HCl, MeOH–$CH_2Cl_2$, reflux; (iv), $Pd(OH)_2$/C, $H_2$, MeOH; (v), pyridine, acetic anhydride.

that existed in a cyclic diacetalic form.[11] The key step in the sequence was a double reductive amination[12,13] of (−)-**5**. Initial attempts to perform the double reductive amination with ammonium acetate at room temperature resulted in the formation of a product mixture from which the desired product could not be isolated. After some experimentation, the use of benzhydrylamine as the nitrogen source, addition of acetic acid (≈2 equiv.), low temperature and slow addition of the amine were all found to help increase the yield of the desired product. These observations can, at least in part, be explained by the hypothesis that initial imine formation and subsequent reduction were fast compared with the cyclisation step. Low concentrations of the amine would therefore help prevent intermolecular nitrogen–carbon bond formation leading to unwanted higher-molecular-mass products.

After the successful incorporation of nitrogen the initial reaction sequence involved the removal of the benzhydryl group before the isopropylidene groups. Although this protocol was successful, removal of the isopropylidene groups was found to be sluggish and difficulties were encountered in purification of the final product (−)-**1**. As a result, it was decided to reverse the order of protecting-group removal. Reaction of (−)-**6** with conc. HCl in MeOH–DCM at reflux for an extended time afforded tetraol (−)-**7** in good yield. The benzhydryl group was then removed *via* catalytic hydrogenolysis to give (−)-**1**[4–7,10]

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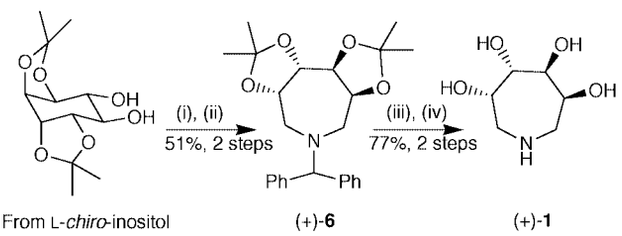
in good yield. Proton and carbon NMR spectra of the free amine (−)-**1** recorded in $D_2O$ were more complex than expected. In light of this result, to further characterise (−)-**1** a small sample was per-acetylated and pentaacetyl compound (−)-**8** was isolated without incident. It was subsequently established that the expected NMR spectra for (−)-**1** could be obtained by recording the sample in 20% DCl–$D_2O$ or 40% NaOD–$D_2O$.

Synthesis of the previously unreported azepane, (3*S*,4*S*,5*S*,6*S*)-3,4,5,6-tetrahydroxyazepane (+)-**1**, was achieved by the same route but starting from L-*chiro*-inositol (Scheme 2).




**Scheme 2** *Reagents and conditions*: (i)–(iv) as for Scheme 1.

In summary we have demonstrated the expedient synthesis of the tetrahydroxyazepanes (+)-**1** and (−)-**1** by a novel route from *chiro*-inositols. Access to both enantiomers should allow some insight into the specificity of tetrahydroxyazepanes as glycosidase inhibitors.

## Experimental

1D-*chiro*-Inositol was prepared on 50–100 g scale by the demethylation[18] of pinitol which was purchased from New Zealand Pharmaceuticals Ltd. 1L-*chiro*-Inositol was similarly prepared from quebrachitol which was purchased from the Rubber Research Institute of Malaysia. NMR spectra were recorded on a Bruker WM-300 instrument (300 MHz for $^1$H and 75 MHz for $^{13}$C), for samples in deuterochloroform (unless otherwise indicated) with tetramethylsilane as internal standard. The multiplicities of the $^1$H signals are indicated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; *etc.* *J*-Values are given in Hz. The multiplicities of $^{13}$C NMR signals were determined by an applied proton test experiment. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. The sample was prepared as a solution in the indicated solvent. Mass spectra were recorded at the Mass Spectrometry unit, Horticulture Research, Palmerston North, New Zealand. Microanalyses were carried out by the staff of the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Mps were determined using a Büchi 510 melting-point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a cell of 1 dm path length. The concentration (*c*) is expressed in g/100 mL (equivalent to g/0.1 L) and $[\alpha]_D$-values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. Analytical TLC was carried out on pre-coated 0.25 mm thick Merck 60 $F_{254}$ silica gel plates. Visualisation was by absorption of UV light, or by thermal development after spraying with basic aq. potassium permanganate or an ethanolic solution of phosphomolybdic acid. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) under a pressure of compressed air. Petroleum spirit refers to the fraction with distillation range 60–80 °C.

### 2,3:4,5-Di-*O*-isopropylidene-D-*manno*-hexodialdose (−)-5[17]

Aq. sodium periodate (5.20 g, 24.3 mmol in 20 mL) was heated, with stirring, to 75 °C over a period of 20 min. Silica (20 g) was added to the stirred solution. The mixture was then cooled and shaken vigorously for 20 min to give a coarse powder. $CH_2Cl_2$ (110 mL) was added and to this stirred mixture was added a solution of 1,2:5,6-di-*O*-isopropylidene-1D-*chiro*-inositol **4** (4.69 g, 18.0 mmol) in $CH_2Cl_2$ (110 mL). The reaction mixture was stirred at RT for 80 min, then filtered and washed with $CH_2Cl_2$. The combined supernatant was concentrated *in vacuo*. The solid was crystallised from ethyl acetate to give (−)-**5** (4.00 g, 86%) as a white solid (Found: C, 55.6; H, 7.2. Calc. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03%); mp 141–142 °C; $[\alpha]_D^{20}$ −57 (*c* 1.6, $CHCl_3$); $\nu_{max}$ ($CDCl_3$)/cm$^{-1}$ 2992, 2939, 1731, 1383, 1249, 1213, 1074; $\delta_H$ 9.66 (2H, s), 4.55 (2H, s), 4.53 (2H, s), 1.58 (6H, s), 1.35 (6H, s); $\delta_C$ 202.0 (CH), 111.8 (C), 80.8 (CH), 76.4 (CH), 26.9 ($CH_3$), 25.4 ($CH_3$).

### (3*R*,4*R*,5*R*,6*R*)-*N*-Benzhydryl-3,4:5,6-bis(isopropylidenedioxy)azepane (−)-6

Acetic acid (2.16 mL, 35.5 mmol) was injected into a stirred mixture of the dialdehyde (−)-**5** (4.68 g, 18.1 mmol), sodium cyanoborohydride (2.49 g, 39.6 mmol) and oven-dried 3 Å molecular sieves (2.90 g) in anhydrous MeOH (300 mL) under argon cooled to −78 °C. Benzhydrylamine (2.83 mL, 16.4 mmol) was then added dropwise to the reaction mixture over a period of 60 min in 6 aliquots. The stirred reaction mixture was warmed to ambient temperature over a period of 15 h. The reaction mixture was filtered through Celite and the Celite washed with ethyl acetate (2 × 200 mL). The combined solvent was then removed *in vacuo*, the remaining residue was taken up in diethyl ether (150 mL), and the extract washed with saturated aq. sodium hydrogen carbonate (80 mL). The aqueous phase was back-extracted with diethyl ether (2 × 100 mL) and the combined organic extract was washed with brine (150 mL) and dried ($MgSO_4$). After filtration the solvent was removed *in vacuo* to give the crude material (6.5 g). Silica gel chromatography and elution with 50–67–100% $CH_2Cl_2$ in petroleum spirit, then 10% ethyl acetate in $CH_2Cl_2$, afforded the *azepane* (−)-**6** (5.28 g, 12.9 mmol, 71%) as a white solid (Found: C, 73.5; H, 7.8; N, 3.4. $C_{25}H_{31}NO_4$ requires C, 73.3; H, 7.63; N, 3.42%); mp 168 °C; $[\alpha]_D^{22}$ −6.8 (*c* 3.0, $CHCl_3$); $\nu_{max}$ ($CDCl_3$)/cm$^{-1}$ 3086, 3064, 3028, 2990, 2938, 2824, 1952, 1898, 1809, 1600, 1492, 1455, 1386, 1260, 1212, 1160, 1047; $\delta_H$ 7.45–7.36 (4H, m), 7.30–7.22 (4H, m), 7.20–7.13 (2H, m), 4.76 (1H, s), 4.42–4.33 (2H, m), 4.26–4.19 (2H, m), 3.15 (2H, dd, *J* 13.3, 2.8), 2.50 (2H, dd, *J* 13.3, 11.4), 1.45 (6H, s), 1.33 (6H, s); $\delta_C$ 142.7 (C), 142.6 (C), 129.2 (CH), 129.1 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 108.7 (C), 79.1 (CH), 74.0 (CH), 72.7 (CH), 50.5 ($CH_2$), 27.4 ($CH_3$), 24.3 ($CH_3$).

### (3*R*,4*R*,5*R*,6*R*)-*N*-Benzhydryl-3,4,5,6-tetrahydroxyazepane (−)-7

Conc. HCl (35 mL) was added dropwise to a stirred solution of (−)-**6** (5.28 g, 12.9 mmol) in MeOH–$CH_2Cl_2$ (2:1; 120 mL). A suspension formed which was heated to reflux, and after 90 min it was noted a solution had formed. After being heated for 48 h the reaction mixture was cooled in an ice-bath and solid $NaHCO_3$ (45 g) was added carefully over a period of 30 min. The mixture was filtered, and concentrated *in vacuo*. The residue was taken up in diethyl ether (200 mL) and the extract washed with saturated aq. $NaHCO_3$ (150 mL). The aqueous phase was back-extracted with further diethyl ether (2 × 200 mL). The combined ethereal extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel chromatography and elution with ethyl acetate, followed by 2.5 and 5% MeOH in ethyl acetate, afforded *tetraol* (−)-**7** (3.79 g, 89%) as a white solid (Found: C, 69.3; H, 7.1; N, 4.2. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25%); mp 135 °C; $[\alpha]_D^{22}$ −87 (*c* 0.86, $CHCl_3$); $\nu_{max}$ ($CDCl_3$)/cm$^{-1}$ 3539, 3086, 3064, 3029, 2890, 2838, 1952, 1893, 1811, 1600, 1453, 1252, 1054; $\delta_H$ ($CD_3OD$) 7.42–7.38 (4H, m), 7.35–7.05 (6H, m), 4.67 (1H, s), 4.07–4.01 (4H, m), 2.80 (2H, dd, *J* 13.2, 5.0), 2.66 (2H, dd, *J* 13.2, 7.5); $\delta_C$ ($CD_3OD$) 144.8 (C), 144.7 (C), 130.1 (CH), 130.0 (CH), 129.6 (CH),

129.4 (CH), 128.6 (CH), 77.6 (CH), 74.1 (CH), 70.9 (CH), 58.3 ($CH_2$).

### (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrahydroxyazepane (−)-1[4–7,10]

Palladium(II) hydroxide on carbon (20% Pd; 43 mg) was added to a stirred solution of (−)-**7** (57 mg, 0.17 mmol) in MeOH (5 mL). The reaction mixture was carefully evacuated (to ≈20 mmHg) and pressurised with hydrogen gas (balloon). After repetition of the procedure five times the reaction mixture was stirred under a hydrogen atmosphere for 16 h, evacuated to remove the hydrogen, then filtered through Celite. The Celite was washed successively with MeOH and water. The combined filtrate was concentrated *in vacuo* and the resultant residue taken up in water (10 mL) and petroleum spirit (10 mL). The aqueous phase was washed with a further portion of petroleum spirit (10 mL), separated, and centrifuged (1500 rpm; 15 min). The supernatant was then concentrated *in vacuo* to give *tetraol* (−)-**1** (26 mg, 94%); $[\alpha]_D^{22}$ −44 (*c* 0.64, $H_2O$, HCl salt) {lit.[10] −38 (*c* 0.5, $H_2O$)}; $\delta_H$ (20% NaOD–$D_2O$) 4.07 (2H, br t, *J* 4.9), 3.94 (2H, br s), 2.93 (2H, dd, *J* 14.4, 3.8), 2.82 (2H, dd, *J* 14.4, 6.6); $\delta_C$ (20% NaOD–$D_2O$) 73.3 (CH), 71.5 (CH), 50.2 ($CH_2$); *m*/*z* (FAB, MeOH–NBA †) 164 [$(M + H)^+$, 100%].

### (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetracetoxy-*N*-acetylazepane (−)-8

Tetraol (−)-**1** (35 mg, 0.21 mmol) in a mixture of pyridine (4 mL) and acetic anhydride (2 mL) was stirred at RT for 14 h. The reaction mixture was diluted with diethyl ether (50 mL) and acidified with 0.1 M HCl (100 mL). The aqueous phase was extracted with further diethyl ether (2 × 50 mL) and the combined ethereal extract was dried ($MgSO_4$). After filtration the solvent was removed *in vacuo* and the residue chromatographed on silica gel. Elution with 30–40–50–100% ethyl acetate–petroleum spirit afforded (−)-**8** (59 mg, 76%); $[\alpha]_D^{22}$ −46 (*c* 0.55, $CHCl_3$); $\nu_{max}$ ($CDCl_3$)/$cm^{-1}$ 2964, 1748, 1654, 1423, 1372, 1234, 1048; $\delta_H$ 5.40–5.30 (4H, m), 3.85–3.70 (4H, m), 2.15 (3H, s), 2.11 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.06 (3H, s); $\delta_C$ 171.3 (C), 170.2 (C), 170.0 (C), 169.9 (C), 169.8 (C), 70.1 (CH), 69.8 (CH), 69.4 (CH), 68.5 (CH), 48.0 ($CH_2$), 44.5 ($CH_2$), 21.9 ($CH_3$), 21.2 ($CH_3$), 21.0 ($CH_3$); *m*/*z* (FAB, NBA–DCM) 374 [$(M + H)^+$, 100%], 314 (20), 286 (15), 133 (20) [Found: $(M + H)^+$, 374.1446. $C_{16}H_{24}NO_9$ requires *m*/*z*, *M*, 374.1451].

Similarly prepared, from L-*chiro*-inositol, were:

### 2,3:4,5-Di-*O*-isopropylidene-L-*manno*-hexodialdose (+)-5[19]

Mp 139 °C; $[\alpha]_D^{20}$ +60 (*c* 1.5, $CHCl_3$); *m*/*z* (EI) 243 [$(M - CH_3)^+$, 5%], 203 (50), 71 (60), 59 (100) (Found: $M^+$, 258.1116. $C_{12}H_{18}O_6$ requires *M*, 258.1103).

† NBA = *m*-nitrobenzyl alcohol.

### (3*S*,4*S*,5*S*,6*S*)-*N*-Benzhydryl-3,4:5,6-bis(isopropylidenedioxy)-azepane (+)-6

(Found: C, 73.3; H, 7.5; N, 3.3. $C_{25}H_{31}NO_4$ requires C, 73.32; H, 7.63; N, 3.42%); mp 166–167 °C; $[\alpha]_D^{20}$ +6.8 (*c* 2.4, $CHCl_3$).

### (3*S*,4*S*,5*S*,6*S*)-*N*-Benzhydryl-3,4,5,6-tetrahydroxyazepane (+)-7

(Found: C, 69.4; H, 6.9; N, 4.2. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25%); mp 134 °C; $[\alpha]_D^{22}$ +90 (*c* 0.86, $CHCl_3$).

### (3*S*,4*S*,5*S*,6*S*)-3,4,5,6-Tetrahydroxyazepane (+)-1

$[\alpha]_D^{20}$ +47 (*c* 0.32, $H_2O$, HCl salt); *m*/*z* (FAB, glycerol–MeOH) 164 [$(M + H)^+$, 100%] [Found: $(M + H)^+$, 164.0915. $C_6H_{14}NO_4$ requires *m*/*z*, 164.0923].

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