Synthesis, glycosidase activity and X-ray crystallography of 3-amino-sugars

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The cleavage of two sugar epoxides, methyl 2,3-anhydro-α-D-mannopyranoside and 2,3-anhydro-α-D-allopyranoside, with amines is presented as a method for preparing a library of 3-amino-sugars (methyl 3-amino-3-deoxy-α-D-altropyranosides and methyl 3-amino-3-deoxy-α-D-glucopyranosides) as potential glycosidase inhibitors. Several of the altropyranosides were micromolar inhibitors of bovine liver β-galactosidase and almond β-glucosidase. X-Ray crystal structures were determined for one of the methyl 3-amino-3-deoxy-α-D-altropyranosides, **4t**, and one of the methyl 3-amino-3-deoxy-α-D-glucopyranosides, **6d**.

Introduction

Glycosidase inhibitors[1] are theraputic targets for several diseases including diabetes, cancer and viral and bacterial infections.[2] Furthermore, β-galactosidase is overexpressed in senescent cells and this has been used as a biomarker of replicative senescence.[3] Senescent cells do not undergo cell division, and are under intensive investigation in research related to the ageing process and cancer.

Many glycosidase inhibitors mimic charge in the transition state of the natural substrate: either the oxocarbenium ion (with the charge assumed to reside either on the endocyclic oxygen or the anomeric carbon) or the conjugate acid of the glycoside in which the exocyclic oxygen is protonated. The introduction of nitrogen atoms is the most common method to mimic this charge. Notable examples of naturally occuring mimics of exocyclic charge[4] are trehalozin, allosamidine, acarbose and mannostatin A.

Library synthesis is a key tool of medicinal chemistry, but simple methods for synthesising libraries of analogous potential glycosidase inhibitors are quite rare. The chemistry available to assemble such libraries is limited to amide coupling,[5] simple imine formation[6] and an approach using a sugar aldehyde in the Strecker reaction.[7] Moreover, the structures of glycosidase inhibitors are often based on iminosugars or aminocyclopentitols, which require several synthetic steps to prepare.

We wished to investigate a different approach to the synthesis of glycosidase inhibitors. Sugar epoxides[8] (*e.g.* 2,3-anhydro sugars) undergo *trans*-diaxial ring opening when treated with amines,[9–14] and our aim was to exploit this green, solvent-free reaction using different amines to give a library of potential glycosidase inhibitors in which the amino group might mimic the protonated form of the exocyclic oxygen.

We present here an investigation of this reaction using simple primary amines and diamines, giving a new method for the synthesis of 3-amino-sugars as potential glycosidase inhibitors.

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Results and discussion

Epoxide cleavage

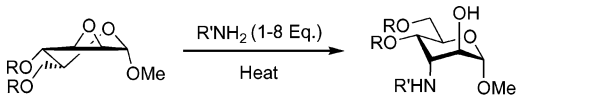
The epoxide, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside **1**, was prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside using an adaptation of the method of Fraser-Reid.[15] Deprotection of **1** in acetic acid gave methyl 2,3-anhydro-α-D-mannopyranoside **2**.[16]

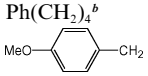
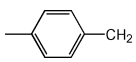
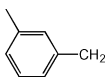
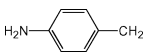
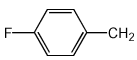
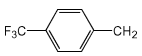
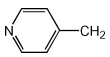
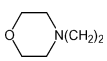
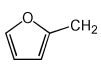
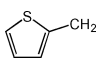
4,6-*O*-Benzylidene-protected epoxide **1** was used in our preliminary investigation. The epoxide was heated in a sealed tube with a 2- or 3-fold excess of the corresponding diamine without solvent to give **3a–c**. The orientation of the addition was confirmed by measurements of coupling constants in the ^{1}H NMR spectrum as the 3-substituted altropyranosides resulting from the expected *trans*-diaxial epoxide cleavage. The protected epoxide **1** is fixed in the $^0H_5$ (half-chair) conformation as depicted in Table 1, which causes the *trans*-diaxial epoxide cleavage to occur exclusively at the 3-position, giving 3-amino-α-D-altropyranoside products.

Next, the deprotected epoxide, methyl 2,3-anhydro-α-D-mannopyranoside **2**, was subjected to the same conditions. Initially, one equivalent or an excess of diamine was used, and the adducts **4a–f** were obtained in moderate yields (Table 1). The reaction was also performed with a range of primary mono-amines to give **4g–v** in good to excellent yields. Again, the products were 3-amino-3-deoxy-α-D-altropyranoside derivatives resulting from *trans*-diaxial cleavage of the $^0H_5$ epoxide. The deprotected epoxide **2** is not conformationally constrained, but only the 3-amino-3-deoxy-altropyranoside resulting from *trans*-diaxial cleavage of the $^0H_5$ epoxide is observed (none of the 2-amino-glucopyranoside that would result from *trans*-diaxial opening of the $^5H_0$ conformer is obtained). The $^4C_1$ conformation was confirmed in the solid state by X-ray crystallographic analysis of **4t** (Fig. 1). On the other hand, the ^{1}H NMR spectra of most of the compounds **4a–v** were consistent with at least a considerable contribution from the $^1C_4$ conformation (*e.g.* **4a**; δ_H (250 MHz, D_2O) 4.71 ppm (1 H, d, *J* 3.6, H-1); *cf.* **3a**; δ_H (250 MHz, $CDCl_3$), 4.60 ppm (1 H, s, H-1), constrained in the $^4C_1$ conformation by the 4,6-*O*-benzylidene protecting group).

The allose epoxide methyl 2,3-anhydro-α-D-allopyranoside **5** was prepared according to the method of Richtmyer[17] and heated

Table 1 Epoxide cleavage of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside **1** and methyl 2,3-anhydro-α-D-mannopyranoside **2** using amines



	R′[a]	Reaction time/h	Temp/°C	Yield (%)
3a	$H_2N(CH_2)_2$[b]	19	100	28
3b	$H_2N(CH_2)_3$[c]	19	100	49
3c	$H_2N(CH_2)_4$[c]	24	100	57
4a	$H_2N(CH_2)_2$[d]	24	120	40
4b	$H_2N(CH_2)_3$[e]	20	100	74
4c	$H_2N(CH_2)_4$[b]	24	120	87
4d	$H_2N(CH_2)_5$[d]	20	120	44
4e	$H_2N(CH_2)_6$[d]	24	110	30
4f	$H_2N(CH_2)_7$[d]	24	110	31
4g	$CH_2{=}CHCH_2$	24	100	92
4h	$CH_3(CH_2)_3$	24	100	92
4i	$HO(CH_2)_4$	24	100	77
4j	$PhCH_2$[d]	19	110	75
4k	$Ph(CH_2)_3$[f]	24	120	68
4l	$Ph(CH_2)_4$[b]	72	125	94
4m		31	100	92
4n		18	100	60
4o		24	100	92
4p		24	100	85
4q		24	100	98
4r		24	100	72
4s		24	100	86
4t		24	100	92
4u		24	100	96
4v		24	100	86

[a] 1.1 Equivalents of amine unless stated otherwise. [b] 3 Equivalents. [c] 4 Equivalents. [d] 1.0 Equivalents. [e] 8 Equivalents. [f] 1.2 Equivalents.

under the above conditions (Table 2) with a range of primary mono-amines. The 3-amino-α-D-glucopyranoside products **6a–d** were obtained in moderate yields and the $^4C_1$ conformation was confirmed for **6d** in the solid state by X-ray crystallography (Fig. 1) and NMR spectroscopy.

Epoxide cleavage of conformationally unconstrained 2,3-anhydro-α-D-allopyranosides generally gives 3-amino-gluco-

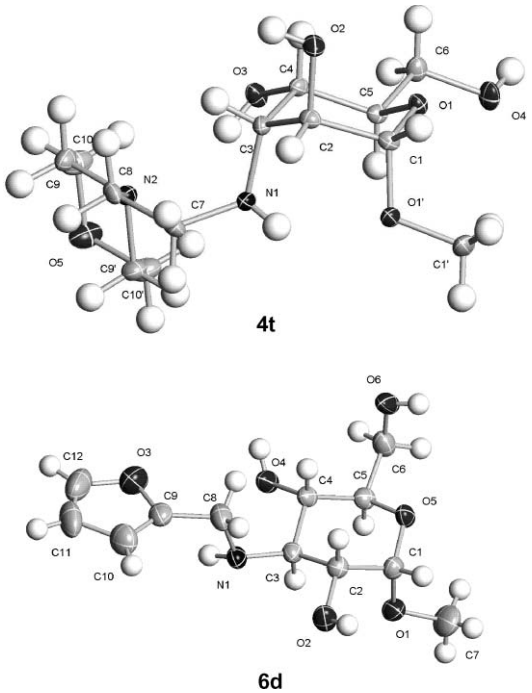
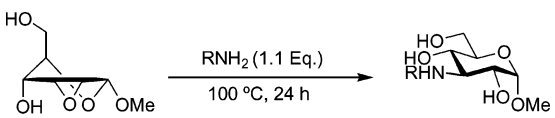
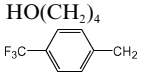
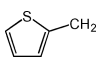
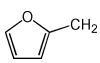


Fig. 1 ORTEP drawings of X-ray structures of **4t** and **6d** showing the atom label scheme and 50% displacement ellipsoids.

Table 2 Epoxide cleavage of methyl 2,3-anhydro-α-D-allopyranoside **5** using amines



	R	Yield (%)
6a	$HO(CH_2)_4$	66
6b		38
6c		65
6d		69

pyranosides. This results from an initially formed $^1C_4$ glucopyranoside due to *trans*-diaxial epoxide cleavage in the $^5H_0$ conformation.[9–11] A ring flip gives the $^4C_1$ conformer. The preference for such reactions to occur in the $^5H_0$ conformation of the epoxide, giving 3-substituted altropyranoside products, has been attributed to the relief of the 1,3-*trans* interaction between the glycosidic methoxy group and H-5,[9] as well as stabilisation of the transition state by hydrogen bonding between the 4-hydroxyl and the epoxide ring oxygen.[11] The outcomes of epoxide cleavage reactions using $HNMe_2$ with **5**[18] and an analagous epoxide in which the 4-hydroxyl is absent[19] do not support this latter hypothesis, since more of the 3-amino adduct (resulting from the

$^5H_0$ conformer) was obtained in the absence of the 4-hydroxyl (a 1 : 1.5 ratio of 2-amino to 3-amino adducts, compared to a 1 : 1 ratio for **5**).

Glycosidase inhibition

Inhibition assays were performed on **4a–v** using bovine liver β-galactosidase, and **4c**, **k** and **l** showed promising results (IC_{50} = 150, 70 and 90 μM respectively). **4h**, **j**, **k**, **l** and **t** also showed a high percentage inhibition of β-glucosidase from almonds (*Prunus* sp.) (76, 80, 76, 86 and 68% respectively at 1 mg mL^{-1}). The compounds were not active against α-glucosidase (*Saccharomyces cerevisiae*), α-galactosidase (green coffee beans), *N*-acetyl-β-glucosamidase (bovine kidney), naringinase (preparation of α-rhamnosidase and approx. 10% β-glucosidase from *Penicillium decumbens*) or α-mannosidase (jack bean, *Canavalia ensiformis*). These results demonstrate the importance of the functionality in the amino side chains of these structures, and it is notable that several of the active compounds bear a phenyl group in this side chain.

The nitrogen atom in this type of glycoside inhibitor might be considered to mimic the protonated form of the exocyclic oxygen atom in the α or β position of the natural substrate, *i.e.* early transition-state analogues. The anomeric selectivity observed (α-glucosidase *vs.* β-glucosidase) is consistent with the previously reported observation that glycosidase inhibitors display anomeric selectivity according to the orientation of the amino group that mimics the anomeric substituent.[20,21] In fact, the extent of this effect depends on the size of the substituent attached to the nitrogen.[22,23] If we assume that our inhibitors are transition state analogues of this type (the amino groups acting as mimics for the protonated form of the exocyclic glycoside oxygen atom) this anomeric selectivity, and, indeed, the fact that glycosidase inhibition was observed at all, supports the NMR evidence (*vide supra*) that, contrary to the $^4C_1$ configuration observed for **4t** in the solid state by X-ray crystalography, these compounds may exist, at least to some extent, as the $^1C_4$ conformers in solution (Fig. 2).

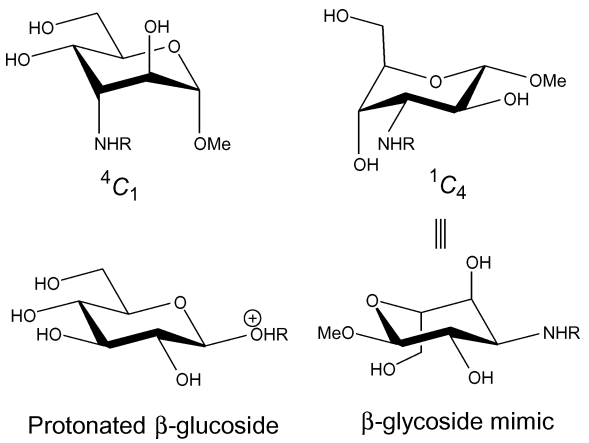


Fig. 2 In their $^1C_4$ conformation, 3-amino-3-deoxy-α-D-altropyranosides mimic protonated β-glycosides.

Conclusions

We have presented the synthesis of 29 potential glycosidase inhibitors using an operationally simple, solvent-free reaction that has potential as a method of preparing larger libraries of glycosidase inhibitors. Evaluation of their activity against glycosidase enzymes revealed some promising results, the best inhibitor being **4k**, for which an IC_{50} value of 70 μM was recorded against β-galactosidase from bovine liver. Current work in our laboratory is aimed at further investigating the potential of this epoxide cleavage reaction.

Experimental

General

Amines were used as received from Aldrich. Flash column chromatography[24] was performed on Sorbil C-60 silica gel (Crossfield Chemicals) 40–60 μm. Thin layer chromatography analysis was conducted on pre-coated, aluminium-backed sheets (60–254) with a 0.2 mm thickness manufactured by Merck and Co. Melting points were measured on a Köfler block and are uncorrected. Infrared spectra were recorded using a Perkin–Elmer FT-IR spectrophotometer, and signals are referred to as strong (s), medium (m), weak (w) or broad (br). Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. NMR spectra were recorded on Bruker ARX 250, AM 300 or DRX 400 spectrometers. Chemical shifts are given in ppm and coupling constants J are given in Hertz (Hz).

Crystal structure determinations

A single crystal of **4t** was obtained by recrystallisation from dichloromethane–methanol, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data: $C_{13}H_{26}N_2O_6$, M = 306.36, orthorhombic, a = 10.2890(1), b = 20.1092(2), c = 7.4282(4) Å, U = 1536.92(9) Å^3, T = 120(2) K, space group $P2_12_12$, Z = 4, absorption coefficient = 0.104 mm^{-1}, 12 656 reflections measured, 2690 unique (R_{int} = 0.0470). The final $wR(F^2)$ was 0.0792 for all data. CCDC reference number 604070. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605916c

A single crystal of **6d** was obtained by recrystallisation from dichloromethane–methanol, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data: $C_{12}H_{19}NO_6$, M = 273.28, monoclinic, a = 9.8736(13), b = 6.0745(8), c = 11.7121(16) Å, U = 651.58(15) Å^3, T = 290(2) K, space group $P2_1$, Z = 2, absorption coefficient = 0.112 mm^{-1}, 4786 reflections measured, 2268 unique (R_{int} = 0.0320). The final $wR(F^2)$ was 0.0792. CCDC reference number 604071. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b605916c

General method for epoxide cleavage

The epoxide and excess amine were placed in a Young's tube and heated. After the specified time, the reaction was cooled and disolved in DCM or methanol. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography using the eluents specified below.

Methyl 3-(2-amino-ethylamino)-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (3a). The general method was followed, using epoxide **1** (824 mg, 3.12 mmol) and ethylenediamine (625 μL, 9.36 mmol), which were heated for 19 h at 100 °C. Column

chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **3a** as an orange oil (278 mg, 28%); $[\alpha]_D^{20}$ +106 (*c* 1.5 in MeOH); ν_{max}(neat)/cm^{-1} 3375w, 2914m, 1660m; δ_H (250 MHz, $CDCl_3$) 2.63–2.80 (3 H, m, H_2NCH_2, HNC*H*H), 2.89–2.99 (1 H, m, HNCH*H*), 3.14 (1 H, s, H-3), 3.36 (3 H, s, OMe), 3.77 (1 H, t, *J* 10.0, 6_{ax}-H), 3.86 (4 H, br s, NH_2, NH, OH), 3.94 (1 H, s, H-2), 4.02–4.14 (2 H, m, H-4, H-5), 4.25–4.30 (1 H, dd, *J* 10.0, 4.5, 6_{eq}-H), 4.60 (1 H, s, H-1), 5.54 (1 H, s, PhC*H*), 7.32–7.37 (3 H, m, Ph), 7.42–7.46 (2 H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 41.4 (CH_2), 48.7 (CH_2), 55.8 (CH_3, OMe), 59.1 (CH, C-3), 59.2 (CH, C-5), 69.3 (CH, C-2), 69.8 (CH_2, C-6), 78.0 (CH, C-4), 102.4 (CH, *C*HPh), 102.9 (CH, C-1), 126.5 (CH, Ph), 128.7 (CH, Ph), 129.4 (CH, Ph), 138.0 (C, Ph); *m*/*z* (FAB) 325 (MH^+, 100%); found MH^+, 325.1764, $C_{16}H_{25}N_2O_5$ requires 325.1764.

Methyl 3-(3-amino-propylamino)-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (3b). The general method was followed using epoxide **1** (788 mg, 2.98 mmol) and 1,3-diaminopropane (995 μL, 11.92 mmol), which were heated for 19 h at 100 °C. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **3b** as an orange oil (490 mg, 49%); $[\alpha]_D^{20}$ +102 (*c* 1.4 in MeOH); ν_{max}(neat)/cm^{-1} 3310w, 2911m, 1627w; δ_H (250 MHz, $CDCl_3$) 1.60 (2 H, app quintet, *J* 6.3, $HNCH_2CH_2$), 2.72–2.89 (4 H, m, $HNCH_2$, H_2NCH_2), 3.13 (1 H, app s, H-3), 3.15–3.27 (4 H, br s, NH_2, NH, OH), 3.35 (3 H, s, OMe), 3.71–3.81 (1 H, m, 6_{ax}-H), 3.93 (1 H, d, *J* 1.6, H-2), 4.04–4.15 (2 H, m, H-4, H-5), 4.26–4.30 (1 H, m, 6_{eq}-H), 4.59 (1 H, s, H-1), 5.56 (1 H, s, PhC*H*), 7.32–7.37 (3 H, m, Ph), 7.43–7.47 (2 H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 32.6 (CH_2), 40.7 (CH_2), 46.9 (CH_2), 55.7 (CH_3, OMe), 59.2 (CH, C-3), 59.3 (CH, C-4), 69.2 (CH, C-2), 69.9 (CH_2, C-6), 78.2 (CH, C-5), 102.5 (CH, CHPh), 103.0 (CH, C-1), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.4 (CH, Ph), 138.2 (C, Ph); *m*/*z* (FAB) 339 (MH^+, 100%); found MH^+, 339.1919, $C_{17}H_{27}N_2O_5$ requires 339.1920.

Methyl 3-(4-amino-butylamino)-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (3c). The general method was followed, using epoxide **1** (1.229 g, 4.66 mol) and 1,4-diaminobutane (1.64 g, 18.64 mmol), which were heated for 24 h at 100 °C. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **3c** as a yellow oil (925 mg, 57%); $[\alpha]_D^{20}$ +98 (*c* 0.9 in MeOH); ν_{max}(neat)/cm^{-1} 3355w, 2927m, 2859m, 1379m, 1099s, 1040s, 967s, 699s; δ_H (250 MHz, $CDCl_3$) 1.59–1.76 (4 H, m, $HNCH_2CH_2$, $H_2NCH_2CH_2$), 2.79–2.89 (2 H, m, $HNCH_2$), 2.90–3.10 (2 H, m, H_2NCH_2), 3.33 (1 H, s, H-3), 3.44 (4 H, br s, NH_2, NH, OH), 3.56 (3 H, s, OMe), 3.97 (1 H, t, *J* 9.6, 6_{ax}-H), 4.12 (1 H, d, *J* 1.6, H-2), 4.22–4.35 (2 H, m, H-4, H-5), 4.49 (1 H, dd, *J* 9.6, 4.6, 6_{eq}-H), 4.76 (1 H, s, H-1), 5.76 (1 H, s, PhC*H*), 7.52–7.58 (3 H, m, Ph), 7.64–7.67 (2 H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 27.8 (CH_2), 31.0 (CH_2), 41.9 (CH_2), 48.8 (CH_2), 55.8 (CH_3, OMe), 59.1 (CH, C-3), 59.2 (CH, C-4), 69.6 (CH, C-2), 69.8 (CH_2, C-6), 78.2 (CH, C-5), 102.5 (CH, CHPh), 102.8 (CH, C-1), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.1 (C, Ph); *m*/*z* (FAB) 353 (MH^+, 100%); found MH^+, 353.2076, $C_{18}H_{29}N_2O_5$ requires 353.2077.

Methyl-3-(2-amino-ethylamino)-3-deoxy-α-D-altropyranoside (4a). The general method was followed, using epoxide **2** (250 mg, 1.42 mmol) and ethylenediamine (95 μL, 1.42 mmol), which were heated at 120 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 1 : 1 v/v) gave **4a** (133 mg, 40%) as a yellow oil; $[\alpha]_D^{20}$ +27 (*c* 0.4 in MeOH); ν_{max}(neat)/cm^{-1} 3360s, 2492m, 1644m, 1449m; δ_H (250 MHz, D_2O) 2.75–2.87 (4 H, m, $NH_2CH_2CH_2NH$, $NH_2CH_2CH_2NH$), 2.92 (1 H, app t, *J* 5.5, H-3), 3.51 (3 H, s, OMe), 3.80–3.95 (4 H, m, H-2, H-5, 2 × H-6), 3.99 (1 H, app t, *J* 5.5, H-4), 4.71 (1 H, d, *J* 3.6, H-1); δ_C (75.7 MHz, D_2O) 40.48 (CH_2), 49.02 (CH_2), 55.85 (CH_3, OMe), 59.36 (CH, C-3), 61.18 (CH_2, C-6), 63.83 (CH, C-2), 68.46 (CH, C-5), 72.76 (CH, C-4), 101.65 (CH, C-1); *m*/*z* (ES) 237 (MH^+, 100%); found MH^+, 237.1450, $C_9H_{21}N_2O_5$ requires 237.1451.

Methyl-3-(3-amino-propylamino)-3-deoxy-α-D-altropyranoside (4b). The general method was followed, using epoxide **2** (209 mg, 1.19 mmol) and 1,3-diaminopropane (825 μL, 9.88 mmol), which were heated at 100 °C for 20 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 1 : 1 v/v) gave **4b** (221 mg, 74%) as a yellow oil; $[\alpha]_D^{20}$ +93 (*c* 0.7 in MeOH); ν_{max}(neat)/cm^{-1} 3301m, 2920m, 1568m; δ_H (400 MHz, D_2O) 1.62 (2 H, app quintet, *J* 7.0, $CH_2CH_2CH_2$), 2.67 (2 H, dd, *J* 7.0, 2.1, CH_2CH_2NH), 2.72 (2 H, app tt, *J* 7.0, 2.1, $NH_2CH_2CH_2$), 2.77 (1 H, app dt, *J* 5.0, 1.3, H-3), 3.37 (3 H, s, OMe), 3.67–3.75 (3 H, m, H-2, 2 × H-6), 3.78 (1 H, dt, *J* 7.0, 3.3, H-5), 3.87 (1 H, dd, *J* 7.0, 5.0, H-4), 4.57 (1 H, d, *J* 3.6, H-1); δ_C (62.9 MHz, D_2O) 30.6 (CH_2), 39.1 (CH_2), 45.4 (CH_2), 55.9 (CH_3, OMe), 59.4 (CH, C-3), 61.2 (CH_2, C-6), 63.9 (CH, C-4), 68.5 (CH, C-2), 72.9 (CH, C-5), 101.7 (CH, C-1); *m*/*z* (FAB) 251 (MH^+, 100%); found MH^+, 251.1607, $C_{10}H_{23}N_2O_5$ requires 251.1607.

Methyl-3-(4-amino-butylamino)-3-deoxy-α-D-altropyranoside (4c). The general method was followed, using epoxide **2** (121 mg, 0.68 mmol) and 1,4-diaminobutane (205 μL, 2.04 mmol), which were heated at 120 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **4c** (155 mg, 87%) as a yellow oil; $[\alpha]_D^{20}$ +50 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3329m, 2925m, 1469m; δ_H (300 MHz, D_2O) 1.18–1.26 (4 H, m, $NHCH_2CH_2CH_2$, $CH_2CH_2NH_2$) 2.35–2.42 (4 H, m, $NHCH_2CH_2$, $CH_2CH_2NH_2$) 2.56 (1 H, dd, *J* 4.5, 1.5, H-3), 3.17 (3 H, s, OMe), 3.45–3.54 (3 H, m, H-2, 2 × H-6), 3.57 (1 H, dd, *J* 7.0, 3.0, H-5), 3.65 (1 H, dd, *J* 7.0, 4.4, H-4), 4.35 (1 H, d, *J* 3.6, H-1); δ_C (75.5 MHz, D_2O) 26.3, 29.2 (2 × CH_2), 40.3 (CH_2), 47.0 (CH_2), 55.5 (CH_3, OMe), 58.9 (CH, C-3), 60.7 (CH_2, C-6), 63.5 (CH, C-4), 68.2 (CH, C-2), 72.7 (CH, C-5), 101.3 (CH, C-1); *m*/*z* (FAB) 265; found MH^+, 265.1764, $C_{11}H_{25}N_2O_5$ requires 265.1763.

Methyl-3-(5-amino-pentylamino)-3-deoxy-α-D-altropyranoside (4d). The general method was followed, using epoxide **2** (230 mg, 1.31 mmol) and 1,5-diaminopentane (154 μL, 1.31 mmol), which were heated at 120 °C for 20 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 1 : 1 v/v) gave **4d** (121 mg, 44%) as a yellow/orange oil; $[\alpha]_D^{20}$ +135 (*c* 1.5 in MeOH); ν_{max}(neat)/cm^{-1} 3325m, 2927m, 2858w, 1568m; δ_H (250 MHz, D_2O) 1.39–1.48 (2 H, m, $HNCH_2CH_2CH_2$), 1.52–1.62 (4 H, m, $HNCH_2CH_2$, $H_2NCH_2CH_2$), 2.68–2.79 (4 H, m, $HNCH_2CH_2$, $H_2NCH_2CH_2$), 2.92 (1 H, dt, *J* 4.0, 1.8, H-3), 3.52 (3 H, s, OMe), 3.83–3.87 (2 H, m, H-6), 3.89 (1 H, d, *J* 3.7, H-2), 3.93 (1 H, dd, *J* 7.0, 3.0, H-5), 4.01 (1 H, dd, *J* 7.0, 4.0, H-4), 4.71 (1 H, d, *J* 3.7, H-1); δ_C (75.7 MHz, D_2O) 24.0 (CH_2), 28.9 (CH_2), 30.9 (CH_2), 40.6 (CH_2), 47.5 (CH_2), 55.9 (CH_3, OMe), 59.3 (CH, C-3), 61.1 (CH_2, C-6), 63.9 (CH, C-2), 68.6 (CH, C-4), 73.1 (CH, C-5), 101.7

(CH, C-1); *m/z* (FAB) 279 (MH^+, 100%); found MH^+, 279.1919, $C_{12}H_{27}N_2O_5$ requires 279.1920.

Methyl-3-(6-amino-hexylamino)-3-deoxy-α-D-altropyranoside (4e). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and hexamethylenediamine (66 mg, 0.57 mmol), which were heated at 110 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **4e** (49 mg, 30%) as a yellow oil; $[\alpha]_D^{20}$ +161 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3327m, 2926s, 1564m, 1464s; δ_H (250 MHz, D_2O) 1.27–1.35 (4 H, m, $HNCH_2CH_2CH_2$, $H_2NCH_2CH_2CH_2$), 1.40–1.54 (4 H, m, $HNCH_2CH_2CH_2$, $H_2NCH_2CH_2CH_2$), 2.55–2.66 (2 H, app q, *J* 3.0, $HNCH_2CH_2$), 2.72–2.81 (3 H, m, H-3, $H_2NCH_2CH_2$), 3.39 (3 H, s, OMe), 3.67–3.73 (2 H, m, 2 × H-6), 3.75 (1 H, d, *J* 3.0, H-2), 3.80 (1 H, dt, *J* 6.7, 3.0, H-5), 3.88 (1 H, dd, *J* 6.7, 4.0, H-4), 4.58 (1 H, d, *J* 3.0, H-1); δ_C (62.9 MHz, D_2O) 26.0 (CH_2), 26.4 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 40.4 (CH_2), 47.5 (CH_2), 55.9 (CH_3, OMe), 59.3 (CH, C-3), 61.2 (CH_2, C-6), 64.0 (CH, C-4), 68.6 (CH, C-2), 73.2 (CH, C-5), 101.7 (CH, C-1); *m/z* (FAB) 293 (MH^+, 100%); found MH^+, 293.2077, $C_{13}H_{29}N_2O_5$ requires 293.2076.

Methyl-3-(7-amino-heptylamino)-3-deoxy-α-D-altropyranoside (4f). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 1,7-diaminoheptane (74 mg, 0.57 mmol), which were heated at 110 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **4f** (55 mg, 31%) as a yellow oil; $[\alpha]_D^{20}$ +61 (*c* 1.2 in MeOH); ν_{max}(neat)/cm^{-1} 3329m, 2919m, 2849m, 1646s, 1260w; δ_H (250 MHz, D_2O) 1.29 (6H, m, $HNCH_2CH_2CH_2$, $HNCH_2CH_2CH_2CH_2$, $H_2NCH_2CH_2CH_2$), 1.40–1.52 (4 H, m, $HNCH_2CH_2$, $H_2NCH_2CH_2$), 2.55–2.66 (2 H, m, $H_2NCH_2CH_2$), 2.73 (1 H, t, *J* 7.0, $HNCHCH_2$), 2.79 (1 H, t, *J* 4.0, H-3), 2.95 (1 H, t, *J* 7.0, $HNCHCH_2$), 3.39 (3 H, s, OMe), 3.67–3.74 (2 H, m, 2 × H-6), 3.76 (1 H, d, *J* 3.6, H-2), 3.81 (1 H, ddd, *J* 9.6, 4.0, 2.3, H-5), 3.89 (1 H, dd, *J* 7.0, 4.0, H-4), 4.59 (1 H, d, *J* 3.6, H-1); δ_C (62.9 MHz, D_2O) 26.2 (CH_2), 26.6 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 40.4 (CH_2), 47.6 (CH_2), 55.9 (CH_3, OMe), 59.3 (CH, C-3), 61.2 (CH_2, C-6), 63.9 (CH, C-4), 68.6 (CH, C-2), 73.2 (CH, C-5), 101.7 (CH, C-1); *m/z* (FAB) 307 (MH^+, 68%) 185 (100) 174 (34); found MH^+, 307.2233, $C_{14}H_{31}N_2O_6$ requires 307.2233.

Methyl-3-allylamino-3-deoxy-α-D-altropyranoside (4g). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and allylamine (47 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 17 : 3 v/v) gave **4g** (122 mg, 92%) as a yellow oil; $[\alpha]_D^{20}$ +135 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3334m, 2917m, 1644w; δ_H (250 MHz, C_6D_6) 3.37 (1 H, d, *J* 5.0, H-3), 3.42 (3 H, s, OMe), 3.58 (2 H, dd, *J* 13.8, 6.2, $HNCH_2$), 3.79 (1 H, dt, *J* 10.0, 3.0, H-5), 4.27–4.32 (2 H, m, H-2, H-6), 4.42 (1 H, dd_{ABX}, pseudo *J* 12.0, 3.0, H-6), 4.53 (1 H, dd, *J* 10.0, 5.0, H-4), 5.08 (1 H, s, H-1), 5.31 (1 H, dd, *J* 10.2, 1.6, CH=CHH), 5.43 (1 H, dd, *J* 17.1, 1.6, CH=CHH), 6.09 (1 H, ddt, *J* 17.1, 10.2, 6.2, $CH_2CH=CH_2$); δ_C (62.9 MHz, C_6D_6) 51.8 (CH_2), 55.5 (CH_3, OMe), 59.9 (CH, C-3), 61.8 (CH, C-4), 62.7 (CH_2, C-6), 68.1 (CH, C-2), 70.9 (CH, C-5), 102.6 (CH, C-1), 116.6 (CH_2), 137.7 (CH); *m/z* (FAB) 234 (MH^+, 100%), 202 (40), 160 (20); found MH^+, 234.1342, $C_{10}H_{20}NO_5$ requires 234.1342.

Methyl-3-(butylamino)-3-deoxy-α-D-altropyranoside (4h). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and butylamine (61 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography using dichloromethane–2 M ammonia in methanol (19 : 1 v/v) as the eluent gave **4h** (130 mg, 92%) as an orange oil; $[\alpha]_D^{20}$ +127 (*c* 1.3 in MeOH); ν_{max}(neat)/cm^{-1} 3339m, 2928m; δ_H (250 MHz, C_6D_6) 1.08 (3 H, t, *J* 7.1, CH_3CH_2), 1.45 (2 H, m, *J* 7.1, CH_3CH_2), 1.54–1.64 (2 H, m, $HNCH_2CH_2$), 2.64 (1 H, app quintet, *J* 6.2, HNCHH), 2.94 (1 H, app quintet, *J* 6.2, HNCHH), 3.28 (1 H, app t, *J* 3.8, H-3), 3.39 (3 H, s, OMe), 3.72 (1 H, app dt, *J* 9.9, 3.9, H-5), 4.23–4.27 (2 H, m, H-2, H-6), 4.37 (1 H, dd_{ABX}, pseudo *J* 12.0, 3.9, H-6), 4.47 (1 H, dd, *J* 9.9, 5.2, H-4), 5.03 (1 H, s, H-1); δ_C (62.9 MHz, C_6D_6) 14.5 (CH_3), 21.0 (CH_2), 33.4 (CH_2), 49.0 (CH_2), 55.5 (CH_3, OMe), 60.8 (CH, C-3), 61.6 (CH, C-4), 62.8 (CH_2, C-6), 68.1 (CH, C-2), 70.9 (CH, C-5), 102.6 (CH, C-1); *m/z* (FAB) 250 (MH^+, 100%) 218 (54); found MH^+, 250.1655, $C_{11}H_{24}NO_5$ requires 250.1655.

Methyl-3(4-hydroxy-butylamino)-3-deoxy-α-D-altropyranoside (4i). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 4-amino-1-butanol (57 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **4i** (117 mg, 77%) as a yellow/orange oil; $[\alpha]_D^{20}$ +112 (*c* 1.7 in MeOH); ν_{max}(neat)/cm^{-1} 3331m, 2931m, 2482w; δ_H (250 MHz, D_2O) 1.55–1.71 (4 H, m, $HNCH_2CH_2$, $HOCH_2CH_2$), 2.71–2.85 (2 H, m, $NHCH_2$), 2.93 (1 H, dd, *J* 6.2, 4.4, H-3), 3.52 (3 H, s, OMe), 3.69 (2 H, t, *J* 6.1, $HOCH_2CH_2$), 3.80–3.87 (2 H, m, H-6), 3.88 (1 H, d, *J* 3.0, H-2), 3.93 (1 H, dd, *J* 6.7, 3.0, H-5), 4.02 (1 H, dd, *J* 6.7, 4.4, H-4), 4.71 (1 H, d, *J* 3.0, H-1); δ_C (75.7 MHz, D_2O) 25.8 (CH_2), 29.5 (CH_2), 47.3 (CH_2), 55.8 (CH_3, OMe), 59.2 (CH, C-3), 61.1 (CH_2, C-6), 61.8 (CH_2), 63.8 (CH, C-4), 68.4 (CH, C-2), 73.0 (CH, C-5), 101.6 (CH, C-1); *m/z* (FAB) 266 (MH^+, 100%); found MH^+, 266.1603, $C_{11}H_{24}NO_6$ requires 266.1604.

Methyl-3-(benzylamino)-3-deoxy-α-D-altropyranoside (4j). The general method was followed, using epoxide **2** (182 mg, 1.03 mmol) and benzylamine (113 μL, 1.03 mmol), which were placed in a Young's tube and stirred at 110 °C for 19 h. Column chromatography with dichloromethane–2 M ammonia in methanol (2 : 3 v/v) as the eluent gave **4j** (218 mg, 75%) as a yellow oil; $[\alpha]_D^{20}$ +160 (*c* 0.7 in MeOH); ν_{max}(neat)/cm^{-1} 3323m, 2916m, 1454m; δ_H (250 MHz, D_2O) 2.92 (1 H, t, *J* 5.1, H-3), 3.44 (2 H, s, $PhCH_2NH$), 3.47 (3 H, s, OMe), 3.77–3.94 (5 H, m, H-2, H-4, H-5, 2 × H-6), 4.67 (1 H, d, *J* 3.2, H-1), 7.34–7.48 (5 H, m, Ph); δ_C (62.9 MHz, D_2O) 51.5 (CH_2), 55.8 (CH_3, OMe), 58.3 (CH, C-3), 61.2 (CH_2, C-6), 63.4 (CH, C-4), 68.1 (CH, C-2), 72.5 (CH, C-5), 101.6 (CH, C-1), 127.8 (CH, Ph), 129.0 (CH, Ph), 129.1 (CH, Ph), 140.0 (C, Ph); *m/z* (FAB) 284 (MH^+, 63%) 252 (17) 91 (100); found MH^+, 284.1490, $C_{14}H_{22}NO_5$ requires 284.1499.

Methyl 3-(3-phenyl-1-propylamino)-3-deoxy-α-D-altropyranoside (4k). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 3-phenyl-1-propylamine (90 μL, 0.67 mmol), which were heated at 120 °C for 24 h. Column chromatography (ethyl acetate–2 M ammonia in methanol, 49 : 1 v/v) gave **4k** (120 mg, 68%) as a yellow oil; $[\alpha]_D^{20}$ +56 (*c* 0.8 in MeOH); ν_{max}(neat)/cm^{-1} 3329m, 2926m, 1453m; δ_H (300 MHz, $CDCl_3$) 1.80–1.88 (2 H, m, $HNCH_2CH_2$), 2.55–2.68 (3 H, m, $PhCH_2$, HNCHH), 2.84–2.95 (2 H, m, H-3, HNCHH), 3.50

(3 H, br s, OH), 3.36 (3 H, s, OMe), 3.43–3.49 (2 H, m, H-5, NH), 3.81–3.98 (4 H, m, H-2, H-4, 2 × H-6), 4.65 (1 H, s, H-1), 7.16–7.20 (3 H, m, Ph), 7.25–7.30 (2 H, m, Ph); δ_C (75.5 MHz, $CDCl_3$), 32.0 (CH_2), 33.3 (CH_2), 48.0 (CH_2), 55.4 (CH_3, OMe), 59.7(CH, C-3), 61.1(CH, C-4), 62.3 (CH_2, C-6), 67.2(CH, C-2), 69.7(CH, C-5), 101.7 (CH, C-1), 125.9 (CH, Ph), 128.4 (CH, Ph), 128.4 (CH, Ph), 141.8 (C, Ph); *m/z* (FAB) 312 (MH^+, 26%) found MH^+, 312.1811, $C_{16}H_{26}NO_5$ requires 312.1811.

Methyl 3-(4-phenylbutylamino)-3-deoxy-α-D-altropyranoside (4l). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 4-phenylbutylamine (270 μL, 1.71 mmol), which were heated at 125 °C for 72 h. Column chromatography (ethyl acetate–2 M ammonia in methanol, 7 : 3 v/v) gave **4l** (173 mg, 94%) as a yellow oil; $[a]_D^{20}$ +216 (*c* 1.6 in MeOH); ν_{max}(neat)/cm^{-1} 3334m, 2857m, 1453m; δ_H (300 MHz, $CDCl_3$) 1.52 (2 H, app quintet, *J* 6.8, $PhCH_2CH_2$), 1.65 (2 H, app quintet, *J* 7.5, $HNCH_2CH_2$), 2.47–2.55 (2 H, m, $PhCH_2$), 2.62 (1 H, t, *J* 7.5, HNC*H*H), 2.81–2.90 (2 H, m, H-3, HNCH*H*), 3.17 (3 H, br s, OH), 3.35 (3 H, s, OMe), 3.39–3.45 (2 H, m, H-5, H-6), 3.81–3.89 (4 H, m, H-2, H-4, H-6′, NH), 4.64 (1 H, s, H-1), 7.15–7.19 (3 H, m, Ph), 7.25–7.30 (2 H, m, Ph); δ_C (75.5 MHz, $CDCl_3$) 28.9 (CH_2), 29.6 (CH_2), 35.6 (CH_2), 48.4 (CH_2), 55.4 (CH_3, OMe), 59.6 (CH, C-3), 60.7 (CH, C-4), 61.8 (CH_2, C-6), 66.9 (CH, C-2), 69.8 (CH, C-5), 101.6 (CH, C-1), 125.8 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 142.3 (C, Ph); *m/z* (FAB) 326 (MH^+, 100%) 294 (28); found MH^+, 326.1968, $C_{17}H_{28}NO_5$ requires 326.1968.

Methyl 3-(4-methoxy-benzylamino)-3-deoxy-α-D-altropyranoside (4m). The general method was followed, using epoxide **2** (94 mg, 0.53 mmol) and *p*-methoxybenzylamine (207 μL, 1.59 mmol), which were heated at 100 °C for 31 h. Column chromatography (ethyl acetate—petrol, 4 : 1 v/v, then dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **4m** as a yellow oil (152 mg, 92%); $[a]_D^{20}$ +88 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3332m, 2911m, 2836w, 1611m, 1512s; δ_H (250 MHz, CD_3OD) 3.04 (1 H, app t, *J* 4.2, H-3), 3.56 (3 H, s, OMe), 3.70–3.77 (1 H app dtd, *J* 5.9, 2.9, 2.5, H-5), 3.83–3.94 (3 H, m, H-4, H-6, HNCH*H*), 3.96 (3 H, s, PhOMe), 3.99–4.06 (3 H, m, H-2, H-6′, HNC*H*H), 4.77 (1 H, s, H-1), 7.07 (2 H, d, *J* 8.0, Ph), 7.45 (2 H, d, *J* 8.0, Ph); δ_C (62.9 MHz, CD_3OD) 53.1 (CH_2), 56.1 (CH_3), 56.1 (CH_3), 60.5 (CH, C-3), 63.7 (CH, C-4), 63.9 (CH_2, C-6), 68.9 (CH, C-2), 72.6 (CH, C-5), 103.6 (CH, C-1), 115.4 (CH, Ph), 131.1 (CH, Ph), 133.8 (C, Ph), 160.8 (C, Ph); *m/z* (FAB) 274 (MH^+, 100%); found MH^+, 314.1604, $C_{15}H_{24}NO_6$ requires 314.1604.

Methyl 3-(4-methylbenzylamino)-3-deoxy-α-D-altropyranoside (4n). The general method was followed, using epoxide **2** (215 mg, 1.22 mmol) and *p*-methylbenzylamine (155 μL, 1.22 mmol), which were heated at 100 °C for 18 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 3 : 2 v/v) gave **4n** (216 mg, 60%) as an orange oil; $[a]_D^{20}$ +99 (*c* 0.9 in MeOH); ν_{max}(neat)/cm^{-1} 3335m, 2922m, 1647w, 1450w; δ_H (250 MHz, D_2O) 2.21 (3 H, s, CH_3), 2.98 (1 H, t, *J* 4.6, H-3), 3.42 (3 H, s, OMe), 3.68–3.73 (2 H, m, H-5, HNC*H*H), 3.81–3.97 (5 H, m, H-2, H-4, 2 × H-6, HNCH*H*), 4.72 (1 H, d, *J* 1.8, H-1), 7.07 (2 H, d, *J* 8.0, Ph), 7.23 (2 H, d, *J* 8.0, Ph); δ_C (62.9 MHz, D_2O) 20.8 (CH_3, Me), 51.6 (CH_2), 55.6 (CH_3, OMe), 58.7 (CH, C-3), 61.4 (CH_2, C-6), 62.6 (CH, C-4), 67.4 (CH, C-2), 71.4 (CH, C-5), 101.6 (CH, C-1), 128.7 (CH, Ph), 129.4 (CH, Ph), 136.9 (C, Ph), 137.0 (C, Ph); *m/z* (FAB) 298 (MH^+, 100%); found MH^+, 298.1655, $C_{15}H_{24}NO_5$ requires 298.1655.

Methyl 3-(3-methyl-benzylamino)-3-deoxy-α-D-altropyranoside (4o). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and *m*-methylbenzylamine (78 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 5 : 1 v/v) gave **4o** (153 mg, 92%) as an orange oil; $[a]_D^{20}$ +78 (*c* 1.2 in MeOH); ν_{max}(neat)/cm^{-1} 3333m, 2917m, 2477m, 1645w, 1450m; δ_H (300 MHz, C_6D_6) 2.31 (3 H, s, CH_3), 3.29–3.36 (4 H, br s, OMe, H-3), 3.59–3.69 (1 H, d, *J* 10.0, H-5), 3.77 (1 H, d, *J* 2.6, HNC*H*H), 4.00 (1 H, d, *J* 2.6, HNCH*H*), 4.14 (1 H, d, *J* 10.0, H-6), 4.19–4.29 (2 H, m, H-2, H-6), 4.34–4.41 (1 H, dd, *J* 10.0, 5.0, H-4), 4.96 (1 H, s, H-1), 5.06 (1 H, br s, NH), 7.05 (1 H, d, *J* 5.6, Ph), 7.23–7.33 (3 H, m, Ph); δ_C (62.9 MHz, C_6D_6) 21.8 (CH_3, Me), 53.1 (CH_2), 55.8 (CH_3, OMe), 59.6 (CH, C-3), 61.2 (CH, C-4), 62.3 (CH_2, C-6), 67.3 (CH, C-2), 70.1 (CH, C-5), 102.1 (CH, C-1), 125.7 (CH, Ph), 128.4 (CH, Ph), 128.3 (CH, Ph), 129.5 (CH, Ph), 138.6 (C, Ph), 140.2 (C, Ph); *m/z* (FAB) 298 (MH^+, 51%); found MH^+, 298.1655, $C_{15}H_{24}NO_5$ requires 298.1655.

Methyl 3-(4-amino-benzylamino)-3-deoxy-α-D-altropyranoside (4p). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and *m*-methylbenzylamine (70 μL 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 4 : 1 v/v) gave **4p** (145 mg, 85%) as a brown oil; $[a]_D^{20}$ +99 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3334m, 2919w, 1614m, 1518m; δ_H (250 MHz, $CDCl_3$) 3.00 (1 H, dd, *J* 4.0, 2.0, H-3), 3.58 (3 H, s, OMe), 3.89 (2 H, s, $HNCH_2$), 3.92 (1 H, app t, *J* 3.0, H-2), 3.96–4.04 (4 H, m, H-4, H-5, 2 × H-6 overlap) 4.75 (1 H, d, *J* 3.0, H-1), 6.99 (2 H, d, *J* 8.3, Ph), 7.36 (2 H, d, *J* 8.3, Ph); δ_C (62.9 MHz, $CDCl_3$) 50.8 (CH_2), 55.9 (CH_3, OMe), 58.0 (CH, C-3), 61.2 (CH_2, C-6), 63.6 (CH, C-4), 68.2 (CH, C-2), 72.8 (CH, C-5), 101.7 (CH, C-1), 116.9 (CH, Ph), 130.1 (CH, Ph), 130.6 (C, Ph), 145.8 (C, Ph); *m/z* (FAB) 299 (MH^+, 80%); found MH^+, 299.1606, $C_{14}H_{23}N_2O_5$ requires 299.1607.

Methyl 3-(4-fluoro-benzylamino)-3-deoxy-α-D-altropyranoside (4q). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and *p*-fluorobenzylamine (71 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **4q** (168 mg, 98%) as an orange oil; $[a]_D^{20}$ +96 (*c* 1.4 in MeOH); ν_{max}(neat)/cm^{-1} 3329m, 2911w, 2836w, 1509s; δ_H (250 MHz, $CDCl_3$) 2.93 (1 H, t, *J* 3.8, H-3), 3.32 (3 H, s, OMe), 3.38–3.44 (1 H, dt, *J* 9.6, 3.5, H-5), 3.65 (1 H, d, *J* 12.9, HNC*H*H), 3.75–3.94 (5 H, m, H-2, H-4, 2 × H-6, HNCH*H*), 4.63 (1 H, s, H-1), 6.96–7.04 (2 H, m, Ph), 7.23–7.29 (2 H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 52.3 (CH_2), 55.8 (CH_3, OMe), 59.4 (CH, C-3), 61.3 (CH, C-4), 62.3 (CH_2, C-6), 67.3 (CH, C-2), 70.0 (CH, C-5), 102.1 (CH, C-1), 115.7 (2CH, d, $^2J_{CF}$ 21.0, Ph), 130.2 (CH, d, $^3J_{CF}$ 8.0, Ph), 136.1 (C, d, $^4J_{CF}$ 3.6, Ph), 162.5 (C, d, $^1J_{CF}$ 245.0, Ph); *m/z* (FAB) 302 (MH^+, 100%); found MH^+, 302.1403, $C_{14}H_{21}NO_5F$ requires 302.1404.

Methyl 3-(4-trifluoromethyl-benzylamino)-3-deoxy-α-D-altropyranoside (4r). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and *p*-trifluoromethylbenzylamine (88 μL,

0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **4r** (144 mg, 72%) as an orange/brown oil; $[a]_D^{20}$ +85 (*c* 1.9 in MeOH); ν_{max}(neat)/cm^{-1} 3332w, 2915w, 1619w; δ_H (250 MHz, $CDCl_3$) 2.96 (1 H, t, *J* 3.6, H-3), 3.32 (3 H, s, OMe), 3.42 (1 H, dt, *J* 10.0, 2.7, H-5), 3.59–3.76 (5 H, br m, 3 × OH, NH, HNC*H*H), 3.77–4.04 (5 H, m, H-2, H-4, 2 × H-6, HNCH*H*), 4.63 (1 H, s, H-1), 7.42 (2 H, d, *J* 8.0, Ph), 7.57 (2 H, d, *J* 8.0, Ph); δ_C (62.9 MHz, $CDCl_3$) 52.49 (CH_2), 55.81 (CH_3, OMe), 59.62 (CH, C-3), 61.11 (CH, C-4), 62.07 (CH_2, C-6), 67.24 (CH, C-2), 69.89 (CH, C-5), 101.96 (CH, C-1), 124.5 (C, q, $^1J_{CF}$ 272, CF_3) 125.9 (CH, Ph), 128.9 (CH, Ph), 130.0 (C, q, $^2J_{CF}$ 32, Ph), 144.24 (C, Ph); *m*/*z* (FAB) 352 (MH^+, 88%); found MH^+, 352.1371, $C_{15}H_{21}NO_5F_3$ requires 352.1372.

Methyl 3-(pyridin-4-ylmethylamino)-3-deoxy-α-D-altropyranoside (4s). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 4-(methylamino)pyridine (67 mg, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v → 3 : 2 v/v) gave **4s** (140 mg, 86%) as an orange oil; $[a]_D^{20}$ +78 (*c* 0.9 in MeOH); ν_{max}(neat)/cm^{-1} 3321m, 2917m, 2469w, 1603m, 1418m; δ_H (250 MHz, D_2O) 2.98 (1 H, dt, *J* 3.9, 1.8, H-3), 3.57 (3 H, s, OMe), 3.83–4.11 (7H, m, H-2, H-4, H-5, 2 × H-6, HNCH_2), 4.75 (1 H, d, *J* 3.7, H-1), 7.54–7.59 (2 H, m, Py), 8.57–8.64 (2 H, m, Py); δ_C (62.9 MHz, D_2O) 50.2 (CH_2), 55.9 (CH_3, OMe), 58.5 (CH, C-3), 61.2 (CH_2, C-6), 63.7 (CH, C-4), 68.3 (CH, C-2), 72.6 (CH, C-5), 101.6 (CH, C-1), 124.2 (CH, Py), 149.1 (CH, Py), 150.6 (C, Py); *m*/*z* (FAB) 285 (MH^+, 38%); found MH^+, 285.1451, $C_{13}H_{21}N_2O_5$ requires 285.1451.

Methyl 3-(2-(morpholin-4-yl)ethylamino)-3-deoxy-α-D-altropyranoside (4t). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 4-(2-aminoethyl)morpholine (81 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **4t** (160mg, 92%) as a yellow solid; mp 128–130 °C; $[a]_D^{20}$ +125 (*c* 1.3 in MeOH); ν_{max}(neat)/cm^{-1} 3363m, 2822m; δ_H (250 MHz, $CDCl_3$) 2.28–2.40 (3 H, m, OCH_2CHH, OCH_2CH_2), 2.48–2.64 (4 H, m, HNCH_2, $HNCH_2CH_2$), 2.83 (1 H, t, *J* 4.0, H-3), 2.96–3.08 (1 H, m, OCH_2CHH), 3.37 (3 H, s, OMe), 3.51 (1 H, dt, *J* 9.8, 3.4, H-5), 3.66–3.73 (4 H, m, OCH_2CH_2 × 2) 3.79–3.92 (4 H, m, 2 × H-6, H-2, H-4), 4.64 (1 H, s, H-1); δ_C (62.9 MHz, $CDCl_3$) 44.6 (CH_2), 53.5 (CH_2), 55.6 (CH_3, OMe), 58.1 (CH_2), 59.7 (CH, C-3), 62.3 (CH, C-4), 62.6 (CH_2, C-6), 67.2 (CH_2), 68.3 (CH, C-2), 70.2 (CH, C-5), 102.1 (CH, C-1); *m*/*z* (FAB) 307 (MH^+, 100%) 185 (36); found MH^+, 307.1869, $C_{13}H_{27}N_2O_6$ requires 307.1869.

Methyl 3-(furan-2-ylmethylamino)-3-deoxy-α-D-altropyranoside (4u). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and furfurylamine (55 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **4u** (150 mg, 96%) as a yellow oil; $[a]_D^{20}$ +93 (*c* 1.3 in MeOH); ν_{max}(neat)/cm^{-1} 3356m, 3318m, 2922w; δ_H (300 MHz, C_6D_6) 2.91 (3 H, s, OMe), 2.99 (1 H, s, H-3), 3.12 (1 H app d, *J* 9.9, H-5), AB system centred at 3.53 (2 H, q_{AB}, pseudo *J* 14.0, HNCH_2), 3.68 (1 H, s, H-2), 3.89 (2 H, qd_{ABX}, pseudo *J* 12.0, 3.3, H-6), 4.09 (1 H, dd, *J* 9.9, 4.9, H-4), 4.56 (1 H, s, H-1), 5.94–5.99 (2 H, m, Ar–H), 7.02 (1 H, br s, Ar–H); δ_C (75.7 MHz, C_6D_6) 44.1 (CH_2), 53.7 (CH_3, OMe), 58.2 (CH, C-3), 59.9 (CH, C-4), 60.8 (CH_2, C-6), 66.4 (CH, C-2), 68.8 (CH, C-5), 100.6 (CH, C-1), 106.2 (CH), 109.2 (CH), 140.8 (CH), 152.8 (C); *m*/*z* (FAB) 274 (MH^+, 100%); found MH^+, 274.1291, $C_{12}H_{20}NO_6$ requires 274.1290.

Methyl 3-(thiophen-2-ylmethylamino)-3-deoxy-α-D-altropyranoside (4v). The general method was followed, using epoxide **2** (100 mg, 0.57 mmol) and 2-(methylamino)thiophene (70 mg, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography using dichloromethane–2 M ammonia in methanol (9 : 1 v/v) as the eluent gave **4v** (141 mg, 86%) as an orange oil; $[a]_D^{20}$ +141 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3392m, 2923w; δ_H (250 MHz, C_6D_6) 3.43 (3 H, s, OMe), 3.49 (1 H, app t, *J* 3.5, H-3), 3.78 (1 H, app d, *J* 10.0, H-5), 4.09–4.43 (4 H, m, H-2, H-6, HNCH_2), 4.44 (1 H, dd_{ABX}, pseudo *J* 11.8, 3.5, H-6), 4.57 (1 H, dd, *J* 10.0, 5.1, H-4), 5.09 (1 H, s, H-1), 7.10 (1 H, dd, *J* 5.1, 3.0, Ar–H), 7.17 (1 H, d *J* 3.0, Ar H), 7.25 (1 H, dd, *J* 5.1, 1.2, Ar–H); δ_C (62.9 MHz, C_6D_6) 47.7 (CH_2), 55.5 (CH_3, OMe), 59.9 (CH, C-3), 61.8 (CH, C-4), 62.6 (CH_2, C-6), 67.9 (CH, C-2), 70.7 (CH, C-5), 102.5 (CH, C-1), 125.3 (CH), 126.0 (CH), 127.4 (CH), 144.8 (C); *m*/*z* (FAB) 290 (MH^+, 38%); found MH^+, 290.1062, $C_{12}H_{20}NO_5S$ requires 290.1062.

Methyl 3-(4-hydroxy-butylamino)-3-deoxy-α-D-glucopyranoside (6a). The general method was followed, using epoxide **5** (100 mg, 0.57 mmol) and 4-amino-1-butanol (57 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 7 : 3 v/v) gave **6a** (99 mg, 66%) as a yellow/orange oil; $[a]_D^{20}$ +84 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3318m, 2930m, 2480m, 1452w; δ_H (250 MHz, D_2O) 1.47–1.49 (4 H, m, $HNCH_2CH_2CH_2$, $HNCH_2CH_2CH_2$), 2.72 (2 H, t, *J* 6.7, HNCH_2), 2.76 (1 H, t, *J* 10.0, H-3), 3.33 (1 H, t *J* 10.0, H-4), 3.35 (3 H, s, OMe), 3.47–3.52 (3 H, m, $HOCH_2$, H-2), 3.56 (1 H, ddd, *J* 10.0, 5.3, 2.0, H-5), 3.56 (1 H, dd, *J* 12.0, 5.3, H-6), 3.77 (1 H, dd, *J* 12.0, 2.0, H-6′), 4.67 (1 H, d, *J* 3.5, H-1); δ_C (62.9 MHz, D_2O) 25.91 (CH_2), 29.49 (CH_2), 47.87 (CH_2), 55.46 (CH_3, OMe), 60.81 (CH, C-3), 61.06 (CH_2, C-6), 61.93 (CH_2), 68.64 (CH, C-4), 70.47 (CH, C-2), 72.33(CH, C-5), 99.45 (CH, C-1); *m*/*z* (FAB) 266 (MH^+, 100%) 234 (8), 206 (7); found MH^+, 266.1603, $C_{11}H_{24}NO_6$ requires 266.1604.

Methyl 3-(4-trifluoromethyl-benzylamino)-3-deoxy-α-D-glucopyranoside (6b). The general method was followed, using epoxide **5** (100 mg, 0.57 mmol) and *p*-trifluoromethylbenzylamine (88 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography using dichloromethane–2 M ammonia in methanol (4 : 1 v/v) as the eluent gave **6b** (76 mg, 38%) as a brown oil; $[a]_D^{20}$ +100 (*c* 1.1 in MeOH); ν_{max}(neat)/cm^{-1} 3205w, 2921w, 1324m; δ_H (250 MHz, CD_3OD) 1.74 (1 H, t, *J* 10.0, H-3), 3.95 (1 H, app d, *J* 10.0, H-4), 3.99 (3 H, s, OMe), 4.08 (1 H, dd, *J* 10.0, 3.6, H-2), 4.11–4.17 (1 H, app ddd, *J* 10.0, 5.0, 2.0, H-5), 4.25 (1 H, dd, *J* 11.7, 5.0, H-6), 4.39 (1 H, dd, *J* 11.7, 2.0, H-6′), 4.69 (2 H, s, HNCH_2), 5.22 (1 H, d, *J* 3.6, H-1), 8.12–8.21 (4 H, m, Ph); δ_C (62.9 MHz, CD_3OD) 52.4 (CH_2), 54.5 (CH_3, OMe), 61.2 (CH, C-3), 61.6 (CH_2, C-6), 69.8 (CH, C-4), 71.9 (CH, C-2), 72.8 (CH, C-5), 99.8 (CH, C-1), 124.7 (C, $^1J_{CF}$ 271, CF_3) 125.2 (CH, $^3J_{CF}$ 3.8, Ph), 129.0 (CH, Ph), 129.2 (C, $^2J_{CF}$ 29.2, Ph), 145.1

(C, Ph); *m/z* (FAB) 352 (MH^+, 100%); found MH^+, 352.1372, $C_{15}H_{21}NO_5F_3$ requires 352.1372.

Methyl 3-(thiophen-2-ylmethyl-amino)-3-deoxy-α-D-glucopyranoside (6c). The general method was followed, using epoxide **5** (100 mg, 0.57 mmol) and 2-(methylamino)thiophene (70 mg, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography (dichloromethane–2 M ammonia in methanol, 9 : 1 v/v) gave **6c** (107 mg, 65%) as a yellow oil; $[\alpha]_D^{20}$ +99 (*c* 1.3 in MeOH); ν_{max}(neat)/cm^{-1} 3398w, 2891w, 2582w; δ_H (250 MHz, D_2O) 2.91 (1 H, t, *J* 9.9, H-3), 3.34–3.44 (4 H, m, OMe, H-4), 3.57 (1 H, dd, *J* 10.3, 3.7, H-2), 3.57–3.63 (1 H, m, H-5), 3.70 (1 H, dd, *J* 12.0, 5.3, H-6), 3.83 (1 H, dd, *J* 12.0, 2.2, H-6′), 4.17 (2 H, s, HNCH_2), 4.72 (1 H, d, *J* 3.7, H-1), 7.01–7.04 (2 H, m, SC=C*H*, SC=CHC*H*=CH), 7.36 (1 H, dd, *J* 5.0, 1.4, SC*H*); δ_C (62.9 MHz, D_2O) 46.7 (CH_2), 55.5 (CH_3, OMe), 59.7 (CH, C-3), 61.1 (CH_2, C-6), 69.2 (CH, C-4), 71.0 (CH, C-5), 72.2 (CH, C-2), 99.4 (CH, C-1), 125.8 (CH), 126.9 (CH), 127.6 (CH), 142.7 (C); *m/z* (FAB) 290 (MH^+, 22%); found MH^+, 290.1062. $C_{12}H_{20}NO_5S$ requires 290.1062.

Methyl 3-(furan-2-ylmethylamino)-3-deoxy-α-D-glucopyranoside (6d). The general method was followed, using epoxide **5** (100 mg, 0.57 mmol) and furfurylamine (55 μL, 0.62 mmol), which were heated at 100 °C for 24 h. Column chromatography using dichloromethane–2 M ammonia in methanol (4 : 1 v/v) as the eluent gave **6d** (107 mg, 69%) as an orange solid; mp 63–65 °C; $[\alpha]_D^{20}$ +80 (*c* 0.8 in MeOH); ν_{max}(neat)/cm^{-1} 3335m, 3207m, 2928m; δ_H (250 MHz, D_2O) 2.98 (1 H, t, *J* 10.0, H-3), 3.51 (1 H, t, *J* 10.0, H-4), 3.52 (H, s, OMe), 3.68 (1 H, dd, *J* 10.4, 3.6, H-2), 3.69–3.76 (1 H, ddd, *J* 10.0, 5.4, 2.3, H-5), 3.83 (1 H, dd, *J* 12.0, 5.4, H-6), 3.95 (1 H, dd, J 12.0, 2.3, H-6′), 4.09 (2 H, s, 2 × NHCH_2), 4.85 (1 H, d, *J* 3.6, H-1), 6.44 (1 H, d, *J* 3.2, Ar–H), 6.54 (1 H, dd, *J* 3.2, 2.0, Ar–H), 7.59 (1 H, d, *J* 2.0, Ar–H); δ_C (62.9 MHz, D_2O) 44.7 (CH_2), 55.5 (CH_3, OMe), 59.6 (CH, C-3), 61.0 (CH_2, C-6), 69.1 (CH, C-4), 71.0 (CH, C-2), 72.2 (CH, C-5), 99.4 (CH, C-1), 108.2 (CH), 110.8 (CH), 143.0 (CH), 153.3 (C_q); *m/z* (FAB) 274 (MH^+, 100%); found MH^+, 274.1291, $C_{12}H_{20}NO_6$ requires 274.1291.

Glycosidase inhibition

All enzymes and substrates were purchased from Sigma. Enzyme and substrate solutions were made using 0.2 M sodium phosphate buffers at suitable pH and protein concentrations (pH 6.5 and 0.2 U mL^{-1} for α-galactosidase (green coffee beans), pH 7.3 and 2.0 U mL^{-1} for β-galactosidase (bovine liver), pH 6.0 and 1.5 U mL^{-1} for α-glucosidase (*Saccharomyces cerevisiae*), pH 5.0 and 0.2 U mL^{-1} for β-glucosidase (almond, *Prunus* sp.), pH 4.5 and 0.2 U mL^{-1} for α-mannosidase (jack bean, *Canavalia ensiformis*), pH 4.0 and 1.0 U mL^{-1} for naringinase (*Penicillium decumbens*) and pH 4.25 and 0.2 UmL^{-1} for *N*-acetyl-β-D-glucosaminidase (bovine kidney)). PNP-glycosides were used as substrates at a concentration of 5 mM.

Compounds tested for enzyme inhibition were disolved in distilled water at a concentration of 1 mg mL^{-1}. Where required, compounds wre dissolved in methanol (*ca.* 20 μL) before dilution using distilled water. Inhibitor solutions were stored at −20 °C. All assays were carried out in triplicate using water as a blank in place of the inhibitor. Reaction time was determined based on the length of time needed to give a final absorbance of 0.3–1.5 units. Linearity of the reaction time course was checked using a series of incubation times. Rate of colour development after the addition of Trinder glucose reagent was determined using a linear time course.

Enzyme solution (10 μL) inhibitor solution (10 μL) and substrate solution (50 μL) were combined in the well of a flat-bottomed 96-well (300 μL) microtitre plate. The reaction mixture was incubated at 25 °C for 5–20 min and was stopped using glycine solution (70 μL, 0.4 M, adjusted to pH 10.4 using NaOH). Absorbance at 405 nm was measured immediately in a microtitre plate reader (Molecular Devices VersaMax microplate reader). Percentage activity was calculated by reference to the control reaction for each assay and percentage inhibition determined by subtraction from 100%.

For IC_{50} determinations, the inhibitors were serially diluted, starting with a tenfold series (0.1–0.0001 mg mL^{-1}) to establish the approximate range, and then diluted within a selected range. IC_{50} values were taken from the resulting curve of percentage absorbance (relative to an uninhibited control) *vs.* concentration.

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