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Synthetic entry to functionalised morpholines and [1,4]-oxazepanes via reductive amination reactions of carbohydrate derived dialdehydes

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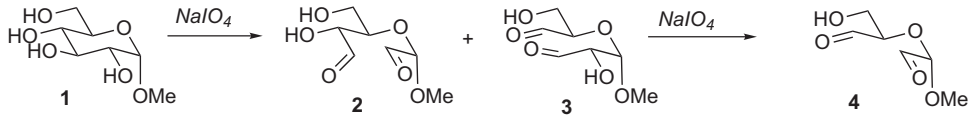
Abstract—The rapid synthesis of functionalised morpholines and [1,4]-oxazepanes displaying up to three stereocentres, by reductive amination reactions between carbohydrate derived dialdehydes and a range of amines, is described.

1. Introduction

The synthetic utility of carbohydrates as inexpensive and readily available, stereodefined starting materials for syntheses programmes has been well recognised and exploited in the chemical literature.[1] In particular, carbohydrates have been utilised for the generation of dialdehydes, via oxidative cleavage of 1,2-diol pairs using $NaIO_4$.[2] If a carbohydrate contains a C-2,3-4 triol moiety, as found within methyl α-D-glucopyranoside **1**, it is recognised that oxidation occurs twice in the presence of excess $NaIO_4$ to yield dialdehyde **4** via dialdehydes **2** and **3** (Scheme 1).

The oxidative cleavage reactions generally occur readily at room temperature and the dialdehydes thus formed are believed to exist in equilibrium in aqueous solution as a number of cyclic and acyclic species.[2] The synthetic versatility of this transformation is reflected by its incorporation within a range of synthetic pathways that have allowed entry to a variety of targets including an anti-herpetic agent,[3] a glycosidase inhibitor containing the 3-oxagranatane skeleton,[4] the methyl ester of leukotriene A_4,[5] and substituted tetrahydrofurans.[6] As part of a programme directed towards the synthesis of novel carbohydrate-based therapeutics,[7] we were interested in developing methodology that would allow rapid entry to functionalised [1,4] oxazepanes and morpholines.[8] Recent literature reports have suggested that such targets may offer potential as anti-fungal[9] and anti-viral[10] agents and as inhibitors of the glycosidase enzymes.[11] [1,4] Oxazepanes are also important components of skeleta of interesting natural products, such as the neurotoxin batrachotoxin.[12] The work reported herein details strategies that have allowed selective entry to either morpholines, 7-hydroxymethyl-[1,4]-oxazepanes or 7-alkoxy-[1,4]-oxazepanes, via reductive amination reactions[13] of dialdehydes generated from methyl α-D-glucopyranosides. This has proved possible via control of the oxidative cleavage of the diol pairs within the glucopyranoside starting material.

Of particular relevance to this work is the report that morpholino glycopeptides can be prepared via reductive



Scheme 1.

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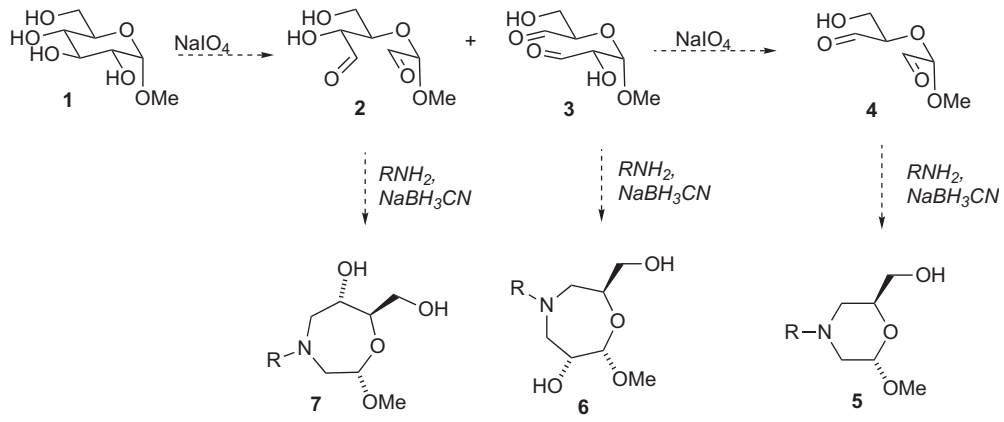


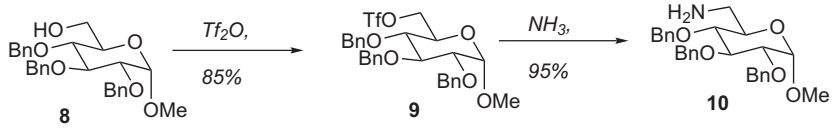
Scheme 2.

amination reactions between carbohydrate derived dialdehydes and amines.[14] Herein we report an investigation into a modification of this procedure, which has probed the efficiency of this reaction for entry to stereodefined, functionalised [1,4]-oxazepanes **6** and **7** by careful control of the sodium periodate ring cleavage reaction of methyl α-D-glucopyranoside, as illustrated in Scheme 2.

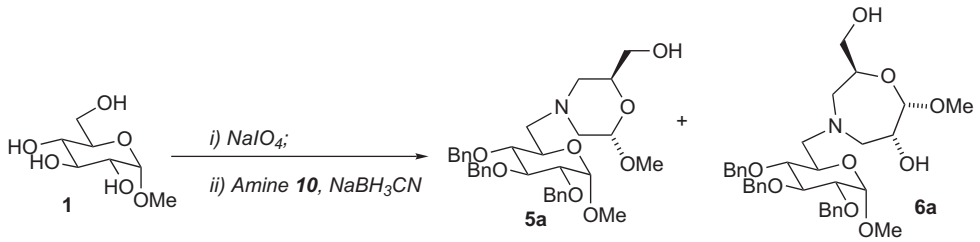
2. Results and discussion

Before selective formation of dialdehydes **2** and **3** was attempted, synthetic entry to a range of morpholines **5** was investigated. In particular, the reaction of dialdehyde **4** with the carbohydrate derived amine **10** was investigated to potentially allow access to a morpholino pseudo-disaccharide. Pseudo-disaccharides have proved to be of interest as glycosidase inhibitors with enhanced specificities compared with monosaccharide inhibitors due to their rich display of hydroxyl functionalities.[15] Carbohydrate amine **10** was prepared in 95% yield by treatment of triflate **9** with ammonia gas in dichloromethane at −15 °C. Triflate **9** was itself prepared in 85% yield by reaction of alcohol **8** with triflic anhydride and pyridine (Scheme 3).[16]

For initial studies, methyl α-D-glucopyranoside was treated with $NaIO_4$ (2 molar equivalents) in methanol at 0 °C and then at room temperature for 3 h to effect dialdehyde formation. Although purification of the intermediate dialdehyde was attempted using C18 reverse phase chromatography, as described by Hindsgaul[14] for the purification of the analogous dialdehyde derived from octyl β-D-glucopyranoside, complete separation of the dialdehyde from the inorganic impurities proved unsuccessful. Therefore, subsequent work-up of the dialdehyde involved concentration of the reaction mixture in vacuo followed by suspension of the resulting colourless solid in ethyl acetate. The suspension was then filtered through Celite and the filtrate concentrated in vacuo to yield the crude dialdehyde as a clear oil. Amine (1 equiv) and sodium cyanoborohydride (5 equiv) were then added to the crude dialdehyde (3 equiv) in methanol containing 10 Å powdered molecular sieves and the reaction stirred at room temperature for 4 h. Interestingly, work-up of the reaction mixture illustrated that both morpholine **5a** and 7-methoxy-[1,4]-oxazepane **6a** had been formed in a 1:1 ratio in 58%, suggesting that incomplete formation of dialdehyde **4** had occurred (Scheme 4). This was despite the reaction conditions that should effect further cleavage of the 1,2-diol within intermediate dialdehyde **3**.



Scheme 3.



Scheme 4.

Table 1. Selective entry to functionalised morpholines **5**

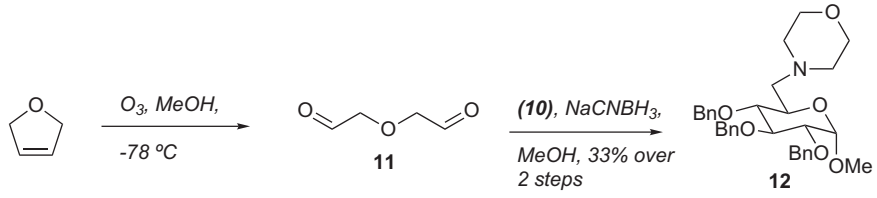
Primary amine	Morpholine **5**, %	7-Methoxy-[1,4]-oxazepane **6**, %
Glucose amine **10**	**5a**, 32	**6a**, 7
Benzylamine	**5b**, 33	**6b**, —
L-Phenylalanine methyl ester	**5c**, 29	**6c**, —

Moreover, since isomeric 7-hydroxymethyl-[1,4]-oxazepane **7** had not been isolated, formation of dialdehyde **2** could not be considered to be a competing reaction. However, increasing the molar equivalents of $NaIO_4$ to 5 and extending the duration of the dialdehyde forming reaction to 15 h biased the reaction to the formation of the morpholine product **5a** in 32%, with only 7% of the oxazepane product **6a** resulting. These conditions were then extended to investigate the reaction of two other amines, namely benzylamine and L-phenylalanine methyl ester with the dialdehyde, to form morpholines **5b** and **c**. The latter was selected for incorporation within the methodology to potentially allow access to analogues of glycosyl amino acids.[17] Pleasingly, in all cases it proved possible to isolate the morpholines in preference to the 7-methoxy-[1,4]-oxazepane products **6b** and **c**, albeit in moderate yields, after work-up and careful purification by column chromatography on silica gel (Table 1). It should be noted that the morpholines were formed as single isomers in one synthetic step from commercially available starting material without the need for any hydroxyl protecting groups.

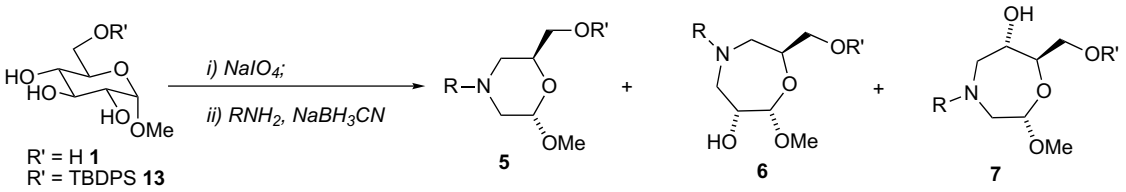
As there was no evidence for the formation of by-products or recovery of methyl α-D-glucopyranoside from the reaction mixtures, the aqueous phase collected during the extraction procedure was analysed, after lyophilisation. This again failed to afford any useful information as to why the yields of the reactions were moderate. Attempts were made to further improve the yield of this reaction but this proved particularly difficult—analysis of the crude dialdehyde mixture to ascertain the exact proportion of dialdehydes present is difficult due to the complex equilibrium that exists between the cyclic and acyclic forms of the dialdehydes under aqueous conditions. Model studies were, therefore, performed that involved the sodium cyanoborohydride mediated reductive amination reaction between a less functionalised glutaric dialdehyde **11**[18] (formed under nonaqueous conditions) and glucose amine **10** to ascertain whether the formation and stability of dialdehyde **4** was a limiting factor. Thus 2,5-dihydrofuran was treated with ozone in methanol at −78 °C to allow in situ generation of aldehyde **11**. The subsequent reductive amination reaction then afforded the morpholine **12** in 33% (Scheme 5); this yield compares closely with that obtained for the synthesis of morpholines **5** from dialdehyde **4**. It was, therefore, concluded that the generation of dialdehyde **4** was unlikely to be the limiting step in the synthetic process.

Since the formation of small quantities of 7-methoxy-[1,4]-oxazepanes **6** had occurred in the strategy above, we next sought to investigate whether conditions could be found that favoured formation of the latter. Thus limited equivalents of $NaIO_4$ (1.2 molar equivalents) were utilised for effecting diol cleavage and the reaction time decreased from 24 h to 4 h, in an attempt to favour formation of dialdehyde **3** over dialdehyde **4**. This indeed proved successful and subsequent reductive amination reactions with the same range of amines as described for entry to morpholines **5**, in the presence of sodium cyanoborohydride, allowed entry to the desired 7-alkoxy-oxazepanes **6** with good selectivities (Scheme 6, Table 2). Again, although the reactions proceeded in only moderate yield, entry to single isomers of the highly substituted, polyfunctionalised 7-methoxy-[1,4]-oxazepanes **6** proved possible in a concise fashion from commercially available starting materials. Attempts were also made to bias the reaction to allow formation of dialdehyde **2**, and thus allow eventual access to the isomeric 7-hydroxymethyl-[1,4]-oxazepanes **7**. Thus a bulky silyl ether protecting group was incorporated at the C-6 hydroxyl group of methyl α-D-glucopyranoside[19] to potentially minimise sodium periodate mediated cleavage of the C-3, C-4 hydroxyl pair. However, when triol **13** was treated with 1.2 molar equivalents of $NaIO_4$ in water/methanol for 4 h, and the resulting dialdehydes treated with the amine and 5 molar equivalents of sodium cyanoborohydride, the 7-methoxy-[1,4]-oxazepane isomers **6** were still formed in preference to the isomeric 7-hydroxymethyl-[1,4]-oxazepanes **7** (Scheme 6, Table 2). The selectivity of the reaction to form the 7-methoxy-[1,4]-oxazepanes **6** was particularly prominent when the sterically hindered amines L-phenylalanine methyl ester and glucose amine **10** were utilised in the reaction.

An alternative approach that proved successful for entry to the 7-hydroxymethyl-[1,4]-oxazepanes **7** involved dialdehyde formation from triol **14** via $NaIO_4$ mediated oxidative cleavage of the C-2, C-3 diol pair. Thus when methyl pyranoside **14**[20] was treated with 1.2 molar equivalents of $NaIO_4$ for 1.5 h and the dialdehyde thus



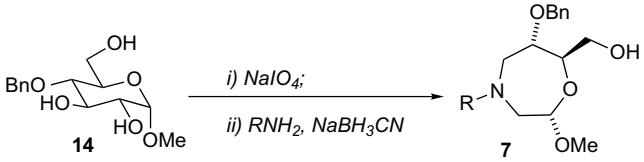
Scheme 5.



Scheme 6.

Table 2. Selective entry to functionalised 7-methoxy-[1,4]-oxazepanes **6**

Primary amine	Methyl α-D-glucopyranoside	Morpholine **5**, %	7-Methoxy-[1,4]-oxazepane **6**, %	7-Hydroxymethyl-[1,4]-oxazepane **7**, %
Glucose amine **10**	**1**	**5a**, —	**6a**, 31	**7a**, —
Benzylamine	**1**	**5b**, 4	**6b**, 21	**7b**, —
L-Phenylalanine methyl ester	**1**	**5c**, 14	**6c**, 26	**7c**, —
Glucose amine **10**	**13**	**5d**, —	**6d**, 30	**7d**, —
Benzylamine	**13**	**5e**, 25	**6e**, 25	**7e**, 7
L-Phenylalanine methyl ester	**13**	**5f**, 1	**6f**, 20	**7f**, —



Scheme 7.

Table 3. Selective entry to functionalised 7-hydroxymethyl-[1,4]-oxazepanes **7**

Primary amine	7-Hydroxymethyl-[1,4]-oxazepane **7**, %
Glucose amine **10**	**7g**, 46
Benzylamine	**7h**, 23
L-Phenylalanine methyl ester	**7i**, 53

formed reacted with amines and sodium cyanoborohydride, the desired 7-hydroxymethyl-[1,4]-oxazepanes **7** were isolated as the only products (Scheme 7, Table 3).

3. Conclusion

In summary, conditions have been described that allow synthetic entry to highly substituted, polyfunctionalised morpholines **5**, 7-methoxy-[1,4]-oxazepanes **6** and 7-hydroxymethyl-[1,4]-oxazepanes **7** from inexpensive and readily available methyl α-D-glucopyranosides. These intermediates may be of use for access to a range of functionalised targets. Chemical elaboration of the targets to allow access to carbohydrate analogues of therapeutic interest is currently being pursued within our laboratories.

4. Experimental procedures

The melting points of all solid products were determined using an Electrothermal digital heated metal block apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Liquid samples were placed between sodium chloride plates as thin films. Frequencies of absorption maxima are reported in wave numbers (cm^{-1}). The following abbreviations are used for the degree of absorption: s (strong), m (medium), w (weak), br (broad). ^1H NMR spectra were recorded at 250 MHz on a Bruker DPX-250 FT-NMR spectrometer or at 400 MHz on a Bruker AMX-400 FT-NMR spectrometer, using $CDCl_3$ or CD_3OD as an internal standard unless stated otherwise. Multiplicities of carbon atoms (methyl, methylene, methine or quaternary) were determined using broadband decoupled carbon spectra and distortionless enhancement by polarisation transfer (DEPT) carbon spectra. All chemical shifts (δ_H and δ_C values) are quoted in units of parts per million (ppm). The following abbreviations are used: s (singlet), d (doublet), t (triplet), dd (double doublet), app. t (apparent triplet), m (multiplet). All coupling constants (J values) are expressed in hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on the spectrometers described above at 63 MHz and 101 MHz and the external reference provided by the solvents $CDCl_3$ or CD_3OD. Low and high resolution mass spectrometry data were recorded using a Fisons VG Autospec, a Micromass Platform LC/MS or a Finnigan MAT900XLT. Molecular ions and fractions from molecular ions are reported as mass/charge (m/z) ratios. Optical activities were determined using a Perkin–Elmer 341 polarimeter at a wavelength of 589 nm and specific rotations are quoted in units of $10^{-1}\,deg\,cm^2\,g^{-1}$. Flash chromatography was performed using silica gel 60 (Merck) using head pressure by means of bellows. TLC analysis was performed using Merck aluminium backed plates, coated with 0.2 mm silica 60 F_{254}. Visualisation of the compounds on the TLC plates was achieved using 254 nm UV light or by using an acid dip ($EtOH–H_2SO_4$, 25:1). All chemicals were obtained from Sigma–Aldrich, BDH, Fluka or Lancaster chemical suppliers and were used as received, unless stated otherwise. For reactions requiring anhydrous condi-

tions, anhydrous solvents were used with glassware oven-dried prior to use and procedures carried out under a nitrogen atmosphere. Elemental analyses were performed by MEDAC Ltd, Brunel Science Centre, Cooper's Hill Lane, Egham, Surrey.

4.1. General method for access to morpholines 5

4.1.1. Step 1: Synthesis of dialdehyde 4. A solution of sodium periodate (5 equiv) in distilled water was added dropwise to a stirred solution of methyl α-D-glucopyranoside (1 equiv) in methanol at 0 °C, and the reaction mixture stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuo and the resulting colourless solid suspended in ethyl acetate, filtered through Celite® and concentrated in vacuo to yield the crude dialdehyde **4** as a clear oil.

4.1.2. Step 2: Reductive amination reaction to afford morpholines 5. Sodium cyanoborohydride (5 equiv) was added to a stirred solution of benzylamine (1 equiv), dialdehyde **4** (3 equiv) and 10 Å molecular sieves in methanol. The pH of the reaction mixture was adjusted to 7 with 2 M HCl (soln Et_2O). After stirring for 24 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was partitioned between H_2O and dichloromethane and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (96:4 CH_2Cl_2–MeOH) to yield the morpholines **5**.

4.2. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-((2*S*,6*S*)-2-hydroxymethyl-6-methoxy-morpholin-4-yl)-α-D-glucopyranoside 5a

By following the general procedure above, sodium cyanoborohydride (30 mg, 0.50 mmol) was added to a stirred solution of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-amino-α-D-glucopyranoside **10** (50 mg, 0.10 mmol), dialdehyde **4** (49 mg, ~0.30 mmol) and 10 Å molecular sieves in methanol (10 mL). Work-up and purification of the residue by flash column chromatography (95:5 CH_2Cl_2–MeOH) afforded morpholine **5a** (19 mg, 0.032 mmol, 32%) as a clear oil; $[\alpha]_D^{20} = +61.5$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3454 (br s, OH), 2927 (s, CH), 1116 (s, C–O), 1054 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.31–7.15 (15H, m, Ph), 4.90 (1H, d, *J* 11.0, $PhCH_2$), 4.85 (1H, d, *J* 11.0, $PhCH_2$), 4.84 (1H, d, *J* 10.0, $PhCH_2$), 4.79 (1H, d, *J* 10.0, $PhCH_2$), 4.67 (1H, d, *J* 11.0, $PhCH_2$), 4.66 (1H, d, *J* 11.0, $PhCH_2$), 4.58 (1H, dd, $J_{5a,6a}$ 11.0 $J_{5a',6a}$ 1.5, C(6a)H), 4.46 (1H, d, $J_{1,2}$ 3.5, C(1)H), 3.99–3.94 (1H, m, C(2a)H), 3.90 (1H, app. t, $J_{2,3}$ $J_{3,4}$ 9.5, C(3)H), 3.80 (1H, ddd, $J_{4,5}$ 8.5 $J_{5,6}$ 1.0 $J_{5,6'}$ 7.5, C(5)H), 3.57 (1H, dd, $J_{2a,7a}$ 1.0 $J_{7a,7a'}$ 12.0, C(7a)H), 3.47 (1H, dd, $J_{2a,7a'}$ 7.5 $J_{7a,7a'}$ 12.0, C(7a′)H), 3.39 (1H, d, $J_{1,2}$ 3.5 $J_{2,2'}$ 10.0, C(2)H), 3.32 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.26–3.20 (1H, m, C(4)H), 2.76 (1H, app. t, $J_{5a,6a}$ $J_{5a,5a'}$) 11.0, C(5a), 2.74 (1H, m, C(3a)H), 2.62 (1H, dd, $J_{5,6}$ 1.0 $J_{6,6'}$ 14.0, C(6)H), 2.43 (1H, dd, $J_{5,6'}$ 7.5 $J_{6,6'}$ 14.0, C(6′)H), 2.31 (1H, dd, $J_{5a',6a}$ 1.5 $J_{5a,5a'}$ 11.0, C(5a′)H), 2.15 (1H, app. t, $J_{3a,3a'}$ $J_{2a,3a'}$ 11.0, C(3a′)H); ^{13}C NMR (63 MHz; $CDCl_3$) 139.1 (ArC), 138.7 (ArC), 138.6 (ArC), 128.9 (ArC), 128.8 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 98.4 (C1), 97.7 (C6a), 82.5 (C3), 80.4 (C2), 79.9 (C4), 76.3 ($PhCH_2O$), 75.4 ($PhCH_2O$), 73.7 ($PhCH_2O$), 69.9 (C5), 69.4 (C2a), 64.6 (C7a), 58.9 (C6), 56.8 (C5a), 56.1 (OCH_3), 55.4 (OCH_3), 55.0 (C3a); *m*/*z* (CI) 594 (37%, $[M+H]^+$), 502 (32%, $[M-PhCH_2]^+$), 380 (26%, $[M-PhCH_2-PhCH_2-OCH_3]^+$), found $[M+H]^+$ 594.3066, $C_{34}H_{44}NO_8$ requires 594.3067.

4.3. (2*S*,6*S*)-4-Benzyl-6-methoxy-morpholin-2-yl-methanol 5b

By following the general procedure above, sodium cyanoborohydride (668 mg, 10.6 mmol) was added to a stirred solution of benzylamine (0.23 mL, 2.11 mmol), dialdehyde **4** (1.02 g, 6.33 mmol) and 10 Å molecular sieves in methanol (20 mL). Work-up and purification by flash column chromatography (96:4 CH_2Cl_2–MeOH) afforded **5b** as a clear oil (163 mg, 0.69 mmol, 33%). $[\alpha]_D^{20} = +91.5$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3422 (br s, OH), 2972 (s, CH), 2850 (s, CH), 1636 (w, C=C), 1317 (s, C–O), 1287 (s, C–O), 1262 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.25–7.14 (5H, m, Ph), 4.62–4.61 (1H, m, C(6)H), 3.99–3.95 (1H, m, C(2)H), 3.57–3.42 (4H, m, C(7,7′)H, $PhCH_2$), 3.32 (3H, s, OCH_3), 2.76 (1H, dd, $J_{5,5'}$ 11.0 $J_{5,6}$ 1.0, C(5)H), 2.62 (1H, dd, $J_{3,3'}$ 11.0 $J_{2,3}$ 2.0, C(3)H), 2.16 (1H, dd, $J_{5,5'}$ 11.0 $J_{5',6}$ 3.0, C(5′)H), 1.98 (1H, at $J_{3,3'}$ $J_{2,3'}$ 11.0, C(3′)H); ^{13}C NMR (63 MHz; $CDCl_3$) 136.9 (ArC), 129.9 (ArC), 128.5 (ArC), 127.7 (ArC), 97.7 (C6), 69.4 (C2), 64.4 ($PhCH_2$), 63.6 (C7), 56.0 (C5), 55.5 (OCH_3), 54.0 (C3); *m*/*z* (CI) 238 (100%, $[M+H]^+$), 206 (30%, $[M-OCH_3]^+$), 91 (51%, $[PhCH_2]^+$), found 238.1445, $C_{13}H_{20}O_3N$ requires 238.1443.

4.4. (2*R*)-((2*S*,6*S*)-2-Hydroxymethyl-6-methoxy-morpholin-4-yl)-3-phenyl-propionic acid methyl ester 5c

By following the general procedure above, sodium cyanoborohydride (63 mg, 1.00 mmol) was added to a stirred solution of L-phenylalanine methyl ester (43 mg, 0.20 mmol), dialdehyde (97 mg, 0.6 mmol) and 10 Å molecular sieves in methanol (20 mL). Work-up and purification of the crude residue by flash column chromatography (6:4 hexane–EtOAc) afforded **5c** (18 mg, 0.058 mmol, 29%) as a clear oil; $[\alpha]_D^{20} = +39.7$ (*c* 0.9, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3436 (br s, OH), 2929 (s, CH), 1731 (s, C=O), 1604 (w, C=C), 1161 (s, C–O), 1058 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.20–7.09 (5H, m, Ph), 4.68–4.66 (1H, m, C(6)H), 4.06–4.01 (1H, m, C(2)H), 3.59–3.52 (1H, m, C(7,7′)H), 3.49 (3H, s, OCH_3), 3.40 (1H, dd, *J* 4.5 *J* 11.0, $PhCH_2CH$), 3.37 (3H, s, OCH_3), 3.07–2.94 (3H, m, $PhCH_2CH$, C(3)H), 2.71 (1H, app. d, $J_{5,5'}$ 11.0, C(5)H), 2.57 (1H, dd, $J_{2,3'}$ 3.0 $J_{3,3'}$ 12.0, C(3′)H), 2.36 (1H, app. t, $J_{5',6}$ $J_{5,5'}$ 11.0, C(5′)H); ^{13}C NMR (63 MHz; $CDCl_3$) 171.7 (CO), 137.8 (ArC), 129.6 (ArC), 128.8 (ArC), 127.0 (ArC), 97.6 (C6), 70.0 ($PhCH_2CH$), 69.5 (C2), 64.3 (C7), 55.6 (OCH_3), 53.3 (C5), 51.5 (OCH_3), 50.6 (C3), 36.3 ($PhCH_2CH$); *m*/*z* (CI) 310 (100%, $[M+H]^+$), 278 (28%, $[M-OCH_3]^+$), 218 (83%, $[M-PhCH_2]^+$), found $[M+H]^+$ 310.1641, $C_{16}H_{24}NO_5$ requires 310.1654.

4.5. General method for access to 7-hydroxymethyl-[1,4]-oxazepanes 6

4.5.1. Step 1: Synthesis of dialdehyde 2. A solution of sodium periodate (1.2 equiv) in distilled water was added dropwise to a stirred solution of methyl α-D-glucopyranoside (1 equiv) in methanol at 0 °C. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo with the resulting colourless solid dissolved in ethyl acetate (100 mL), filtered through Celite® and concentrated in vacuo to yield the crude dialdehyde **2** as a clear oil.

4.5.2. Step 2: Reductive amination reactions to afford 7-hydroxymethyl-[1,4]-oxazepanes 6. Sodium cyanoborohydride (5 equiv) was added to a stirring solution of amine (1 equiv), dialdehyde (3 equiv) and 10 Å molecular sieves in methanol (40 mL). The pH of the reaction mixture was adjusted to 7 with 2 M HCl (soln Et_2O). After stirring for 18 h at room temperature, the reaction mixture was concentrated in vacuo, partitioned between H_2O and dichloromethane (3×100 mL) and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo to yield the [1,4]-oxazepanes **6**.

4.6. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-((2*S*,6*R*,7*S*)-6-hydroxy-2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-4-yl)-α-D-glucopyranoside 6a

By following the general procedure detailed above, sodium cyanoborohydride (198 mg, 3.15 mmol) was added to a stirred solution of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-amino-α-D-glucopyranoside **10** (374 mg, 0.63 mmol), dialdehyde (362 mg, 1.89 mmol) and 10 Å molecular sieves in methanol (40 mL). Work-up and purification of the residue by flash column chromatography (99:1 CH_2Cl_2–MeOH) afforded [1,4]-oxazepane **6a** (122 mg, 0.19 mmol, 31%) as a clear oil; $[\alpha]_D^{20} = +21.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3452 (br s, OH), 2918 (s, CH), 1178 (s, C–O), 1070 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.30–7.16 (15H, m, Ph), 4.92 (1H, d, *J* 11.0, $PhCH_2$), 4.83 (1H, d, *J* 11.0, $PhCH_2$), 4.71 (2H, d, *J* 10.0, $PhCH_2$), 4.57 (1H, d, *J* 11.0, $PhCH_2$), 4.48 (1H, d, $J_{1,2}$ 3.0, C(1)H), 4.47 (1H, d, *J* 11.0, $PhCH_2$), 4.44 (1H, d, $J_{6a,7a}$ 4.0, C(7a)H), 4.05 (1H, dd, $J_{6a,7a}$ $J_{5a,6a}$ 4.0 $J_{5a'6a}$ 9.0, C(6a)H), 3.91 (1H, app. t, $J_{2,3}$ $J_{3,4}$ 9.5, C(3)H), 3.88–3.85 (1H, m, C(2a)H), 3.71 (1H, app. t, $J_{4,5}$ $J_{5,6}$ 9.0, C(5)H), 3.47–3.38 (3H, m, C(2,8a,8a′)H), 3.40 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.08 (1H, app. t, $J_{3,4}$ $J_{4,5}$ 9.0, C(4)H), 2.91 (2H, dd, $J_{5,6}$ $J_{5,6'}$ 1.5, $J_{6,6'}$ 14.0, C(6,6′)H), 2.85–2.76 (3H, m, C(3a,3a′,5a)H), 2.47 (1H, dd, $J_{5a'6a'}$ 9.0 $J_{5a,5a'}$ 13.0, C(5a′)H); ^{13}C NMR (63 MHz; $CDCl_3$) 139.0 (ArC), 138.6 (ArC), 138.4 (ArC), 128.9 (ArC), 128.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 102.8 (C7a), 98.4 (C1), 82.4 (C3), 80.3 (C2, C4), 76.2 ($PhCH_2O$), 75.5 ($PhCH_2O$), 73.8 ($PhCH_2O$), 72.7 (C6a), 69.8 (C5), 69.6 (C2a), 65.1 (C8a), 60.6 (C6), 58.9 (C5a), 56.7 (C3a), 56.6 (OCH_3), 56.1 (OCH_3); *m*/*z* (CI) 624 (100%, $[M+H]^+$), 533 (6%, $[M-PhCH_2]^+$), 410 (6%, $[M-PhCH_2-PhCH_2-OCH_3]^+$), 91 (38%, $[PhCH_2]^+$), found $[M+H]^+$ 624.3170, $C_{35}H_{46}NO_6$ requires $[M+H]^+$ 624.3167.

4.7. (2*S*,6*R*,7*S*)-4-Benzyl-2-hydroxymethyl-7-methoxy-[1,4]-oxazepan-6-ol 6b

By following the general procedure described above, sodium cyanoborohydride (630 mg, 10.0 mmol) was added to a stirring solution of benzylamine (0.22 mL, 2.00 mmol), dialdehyde (1.16 g, 6 mmol) and 10 Å molecular sieves in methanol (40 mL). Work-up and purification by flash column chromatography (96:4 CH_2Cl_2–MeOH) afforded[1,4]-oxazepane **6b** as a clear oil (111 mg, 0.42 mmol, 21%); $[\alpha]_D^{20} = +66.0$ (*c* 0.7, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3402 (br s, OH), 2924 (s, CH), 1172 (s, C–O), 1058 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.40–7.28 (5H, m, Ph), 4.55 (1H, d, $J_{6,7}$ 4.0, C(7)H), 4.23 (1H, m, C(2)H), 4.00 (1H, app. dd, $J_{6,7}$ 4.0 $J_{5.6}$ 6.5, C(6)H), 3.76 (2H, s, $PhCH_2N$), 3.57 (1H, dd, $J_{2,8}$ 4.5 $J_{8,8'}$ 11.0, C(8)H), 3.51 (3H, s, OCH_3), 3.49 (1H, dd, $J_{2,8'}$ 6.0 $J_{8,8'}$ 11.0, C(8′)H), 3.05 (1H, dd, $J_{5,6}$ 6.5 $J_{5,5'}$ 12.5, C(5)H), 2.90 (1H, app. d, $J_{3,3'}$ 12.5, C(3′)H), 2.72 (1H, app. d, $J_{5,5'}$ 12.5, C(5′)H), 2.44 (1H, dd, $J_{2,3}$ 10.0 $J_{2,3'}$ 12.5, C(3)H); ^{13}C NMR (63 MHz; $CDCl_3$) 137.6 (ArC), 129.5 (ArC), 128.8 (ArC), 128.1 (ArC), 102.5 (C7), 72.4 (C2), 69.4 (C6), 64.9 (C8), 63.5 ($PhCH_2$), 58.6 (C3), 56.5 (OCH_3), 54.8 (C5); *m*/*z* (CI) 268 (37%, $[M+H]^+$), 236 (14%, $[M-OCH_3]^+$), 120 (66%, $[PhCHNCH_2]^+$), found $[M+H]^+$ 268.1542, $C_{14}H_{22}NO_4$ requires 268.1549.

4.8. (2*R*)-[(2*S*,6*R*,7*S*)-6-Hydroxy-2-(hydroxymethyl)-7-methoxy-[1,4]-oxazepan-4-yl]-3-phenyl-propionic acid methyl ester 6c

By following the general procedure above, sodium cyanoborohydride (630 mg, 10.0 mmol) was added to a stirred solution of L-phenylalanine methyl ester (432 mg, 2.00 mmol), dialdehyde (1.16 g, 6 mmol) and 10 Å molecular sieves in methanol (40 mL). The reaction mixture was stirred for 19 h at room temperature, then concentrated in vacuo, partitioned between 1 M HCl (100 mL) and dichloromethane (3×100 mL), and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo. Flash column chromatography (94:6 CH_2Cl_2–MeOH) of the residue yielded **6c** (173 mg, 0.52 mmol, 26%) as a clear oil; $[\alpha]_D^{20} = +23.7$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3412 (br s, OH), 2949 (s, CH), 1732 (s, C=O), 1604 (w, C=C), 1173 (s, C–O), 1068 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.34–7.17 (5H, m, Ph), 4.52 (1H, d, $J_{6,7}$ 4.0, C(7)H), 4.19–4.12 (1H, m, C(2)H), 3.97 (1H, app. dd, $J_{5,6}$ $J_{6,7}$ 4.0 $J_{5',6}$ 7.0, C(6)H), 3.72 (1H, dd, *J* 8.0 *J* 12.0, $PhCH_2CH$), 3.70 (3H, s, OCH_3), 3.61–3.49 (2H, m, C(8,8′)H), 3.48 (3H, s, OCH_3), 3.21–3.15 (2H, m, C(5)H, $PhCH_2CH$), 2.96–2.74 (4H, m, C(5′,3,3′)H, $PhCH_2CH$); ^{13}C NMR (63 MHz; $CDCl_3$) 172.6 (CO), 137.7 (ArC), 129.6 (ArC), 128.8 (ArC), 127.2 (ArC), 102.4 (C7), 72.6 (C2), 69.7 ($PhCH_2CH$), 69.4 (C6), 64.7 (C8), 58.2 (C3), 56.4 (OCH_3), 52.2 (OCH_3), 50.5 (C5), 36.5 ($PhCH_2CH$); *m*/*z* (CI) 340 (91%, $[M+H]^+$), 308 (11%, $[M-OCH_3]^+$), 248 (83%, $[M-PhCH_2]^+$), found $[M+H]^+$ 340.1769, $C_{17}H_{26}NO_6$ requires 340.1760.

4.9. Synthesis of glutaric dialdehyde 11

Ozone was bubbled through a stirred solution of 2,5-dihydrofuran (0.17 mL, 2.24 mmol) in anhydrous methanol (40 mL) at −78 °C, which had been previously flushed with nitrogen. Upon the formation of a blue colour, the reaction mixture was flushed with nitrogen until the blue colour disappeared. Dialdehyde **11** was used immediately in situ in subsequent reactions after allowing the solution to warm to room temperature.

4.10. Methyl 6-deoxy-6-(morpholin-4-yl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 12

A stirred solution of glutaric dialdehyde **11** (50 mg, 0.50 mmol) in methanol (50 mL) was synthesised using the above method, to which methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-amino-α-D-glucopyranoside **10** (0.10 g, 0.21 mmol) and powdered 4 Å molecular sieves (10 mg) were added. After 10 min, sodium cyanoborohydride (0.04 g, 0.63 mmol) was added and the reaction mixture stirred for a further 48 h. Upon completion, the reaction mixture was concentrated in vacuo and partitioned between 1 M HCl (50 mL) and dichloromethane (4 × 50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (98:2–9:1 CH_2Cl_2–MeOH) yielded **12** as a clear oil (38 mg, 0.071 mmol, 33%); $[\alpha]_D^{20} = +25.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 2917 (s, CH), 1646 (w, C=C), 1497 (w, C=C), 1454 (w, C=C), 1071 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.28–7.18 (15H, m, Ph), 4.93–4.53 (6H, m, $PhCH_2$), 4.48 (1H, d, $J_{1,2}$ 5.0, C(1)H), 3.88 (1H, app. t, $J_{2,3}$ $J_{3,4}$ 7.5, C(3)H), 3.84–3.70 (1H, m, C(5)H), 3.66–3.58 (2H, m, C(6,6′)H), 3.41 (1H, dd, $J_{1,2}$ 2.5 $J_{2,3}$ 10.0, C(2)H), 3.32–3.25 (4H, m, C(4)H, OCH_3), 2.50–2.33 (8H, m, CH_2); ^{13}C NMR (63 MHz; $CDCl_3$) 139.1 (ArC), 138.9 (ArC), 138.6 (ArC), 128.9 (ArC), 128.8 (ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (ArC), 128.2 (ArC), 128.0 (ArC), 98.3 (C1), 82.5 (C3), 80.4 (C2), 80.3 (C4), 76.3 ($PhCH_2$), 75.5 ($PhCH_2$), 73.8 ($PhCH_2$), 69.1 (C5), 59.8 (C6), 55.8 (OCH_3), 55 (CH_2); *m/z* (CI) 534 (82%, $[M+H]^+$), 442 (23%, $[M-PhCH_2]^+$), 321 (18%, $[M-OCH_3-2PhCH_2]^+$), 91 (100%, $[PhCH_2]^+$), found: $[M+H]^+$ 534.2852, $C_{32}H_{40}NO_6$ requires $[M+H]^+$ 534.2856.

4.11. General method for reductive amination of *O*-TBDPS methyl pyranoside 13

4.11.1. Step 1: Synthesis of dialdehydes. A solution of sodium periodate (1.2 equiv) in distilled water (20 mL) was added dropwise to a stirred solution of methyl 6-*O* *tert* butyldiphenylsilyl-α-D-glucopyranoside **13** (1 equiv) in methanol at 0 °C, and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo and the resulting colourless solid dissolved in ethanol (20 mL), filtered through Celite® and concentrated in vacuo to yield a mixture of crude dialdehydes as a clear oil.

4.11.2. Step 2: Reductive amination reaction. Sodium cyanoborohydride (5 equiv) was added to a stirred solution of amine (1.1 equiv), the dialdehydes (3 equiv) and 10 Å molecular sieves in methanol. The pH was adjusted to 7 by the addition of 5 M HCl in methanol. The reaction mixture was stirred for 41 h at room temperature and then concentrated in vacuo. The residue was partitioned between H_2O and dichloromethane and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo.

4.12. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-[(2*S*,6*R*,7*S*)-2-(*tert*butyldiphenylsilanyloxymethyl)-6-hydroxy-7-methoxy-[1,4]-oxazepan-4-yl]-α-D-glucopyranoside 6d

By following the general procedure above, sodium cyanoborohydride (55 mg, 1.05 mmol) was added to a stirred solution of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-amino-α-D-glucopyranoside **10** (0.10 g, 0.21 mmol), the dialdehydes (234 mg, 0.63 mmol) and 10 Å molecular sieves in methanol (30 mL). Work-up and purification of the residue by flash column chromatography (8:2 hexane–EtOAc) yielded [1,4]-oxazepane **6d** as a clear oil (52 mg, 0.06 mmol, 30%); $[\alpha]_D^{20} = +21.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 1654 (w, C=C), 1454 (w, C=C), 1428 (w, C=C), 1071 (s, C–O); ^{1}H NMR (400 MHz; $CDCl_3$) 7.68–7.13 (25H, m, Ph), 5.00–4.53 (7H, m, C(1)H, 3($PhCH_2$)), 4.42 (1H, d, $J_{6a,7a}$ 2.5, C(7a)H), 4.19–4.12 (1H, m, C(6a)H), 3.98 (1H, app. t, $J_{2,3}$ $J_{3,4}$ 5.0, C(3)H), 4.00–3.95 (1H, m, C(2a)H), 3.80–3.73 (1H, m, C(5)H), 3.58 (1H, dd, $J_{2a,8a}$ 2.5 $J_{8a,8a'}$ 5.0, C(8a)H), 3.47 (1H, dd, $J_{1,2}$ 2.5 $J_{2,3}$ 5.0, C(2)H), 3.42–3.39 (1H, m, C(8a′)H), 3.32 (6H, s, OCH_3), 3.15 (1H, app. t, $J_{3,4}$ $J_{4,5}$ 5.0, C(4)H), 3.09 (1H, app. d, $J_{3a,3a'}$ 5.0, C(3a)H), 2.99 (1H, app. d, $J_{6,6'}$ 7.5, C(6)H), 2.89–2.82 (2H, m, C(5a,5a′)H), 2.53 (1H, dd, $J_{6,6'}$) 7.5, $J_{5,6'}$ 5.0, C(6′)H, 2.41 (1H, dd, $J_{3a,3a'}$ 5.0, $J_{3a',2a}$ 7.5, C(3a′)H, 1.05–1.01 (9H, m, $(C(CH_3)_3)$); ^{13}C NMR (101 MHz; $CDCl_3$) 138.6 (ArC), 137.8 (ArC), 137.0 (ArC), 136.4 (ArC), 135.5 (ArC), 129.7–126.3 (Ph), 102.0 (C7a), 97.9 (C1), 82.0 (C3), 80.0 (C2), 80 (C4), 75.8 ($PhCH_2$), 75.0 ($PhCH_2$), 73.4 ($PhCH_2$), 72.3 (C6a), 69.5 (C5), 69.2 (C2a), 65.5 (C8a), 60.3 (C6), 58.9 (C3a), 56.6 (C5a), 55.9 (OCH_3), 55.6 (OCH_3), 26.8 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); *m/z* (CI) 862 (24%, $[M+H]^+$), 196 (66%, $[CH_2OSiPh_2]^+$), 91 (100%, $[PhCH_2]^+$), found: $[M+H]^+$ 862.4372, $C_{51}H_{64}NO_9$ Si requires $[M+H]^+$ 862.4350.

4.13. (2*S*,6*S*)-4-Benzyl-2-(*tert*butyldiphenylsilanyloxymethyl)-6-methoxy-morpholine 5e, (2*S*,6*R*,7*S*)-4-benzyl-2-(*tert*butyldiphenylsilanyloxymethyl)-7-methoxy-[1,4]-oxazepan-6-ol 6e and (2*S*,6*S*,7*R*)-4-benzyl-7-(*tert*butyldiphenylsilanyloxymethyl)-2-methoxy-[1,4]-oxazepan-6-ol 7e

By following the general procedure above, sodium cyanoborohydride (255 mg, 4.05 mmol) was added to a stirred solution of benzylamine (0.09 mL, 0.81 mmol), the dialdehydes (1.05 g, 2.43 mmol) and 10 Å molecular sieves in methanol (40 mL). Work-up and purification of the residue by flash column chromatography (9:1–6:4 hexane–EtOAc) yielded **5e** (95 mg, 0.29 mmol, 25%), **6e** (101 mg, 0.20 mmol, 25%) and **7e** (28 mg, 0.056 mmol, 7%) as clear oils.

Compound **5e**: $[\alpha]_D^{20} = +72.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 2924 (s, CH), 1611 (w, C=C), 1114 (s, C–O), 1047 (s, C–O); ^1H NMR (400 MHz; $CDCl_3$) 7.59–7.54 (5H, m, Ph), 7.37–7.16 (10H, m, Ph), 4.65–4.64 (1H, m, C(6)H), 4.12–4.09 (1H, m, C(2)H), 3.70 (1H, dd, $J_{2,7}$ 5.0 $J_{7,7'}$ 10.0, C(7)H), 3.58 (1H, dd, $J_{2,7'}$ 5.0 $J_{7,7'}$ 10.0, C(7′)H), 3.53 (2H, s, $PhCH_2N$), 3.38 (3H, s, OCH_3), 2.89–2.83 (2H, m, C(3,5)H), 2.20 (1H, dd, $J_{5,5'}$ 11.0 $J_{5',6}$ 3.0, C(5′)H), 1.93 (1H, app. t, $J_{2,3'}$ $J_{3,3'}$ 11.0, C(3′)H), 1.02 (9H, s, $C(CH_3)_3$); ^{13}C NMR (101 MHz; $CDCl_3$) 136.7 (ArC), 135.8 (ArC), 134.3 (ArC), 129.7 (ArC), 129.1 (ArC), 128.7 (ArC), 128.2 (ArC), 127.9 (ArC), 127.7 (ArC), 127.2 (ArC), 97.2 (C6), 69.1 (C2), 65.2 (C7), 63.4 ($PhCH_2N$), 55.7 (C5), 55.0 (C3), 54.8 (OCH_3), 26.8 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); *m/z* (CI) 476 (65%, $[M+H]^+$), 446 (42%, $[M-OCH_3]^+$), 220 (41%, $[M-OSi(Ph_2)C(CH_3)_3]^+$), found $[M+H]^+$ 476.2633, $C_{29}H_{38}NO_3Si$ requires 476.2621.

Compound **6e**: $[\alpha]_D^{20} = +71.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3325 (br s, OH), 2930 (s, CH), 1173 (s, C–O), 1063 (s, C–O); ^1H NMR (250 MHz; $CDCl_3$) 7.53–7.17 (15H, m, Ph), 4.37 (1H, d, $J_{6,7}$ 4.0, C(7)H), 4.15–4.05 (1H, m, C(2)H), 3.88 (1H, app. dd, $J_{6,7}$ 4.0 $J_{5,6}$ 7.0, C(6)H), 3.69 (1H, d, *J* 13.0, $PhCH_2N$), 3.60 (1H, d, *J* 13.0, $PhCH_2N$), 4.52 (1H, dd, $J_{2,8}$ 5.0 $J_{8,8'}$ 10.0, C(8)H), 3.31 (1H, dd, $J_{2,8'}$ 7.0 $J_{8,8'}$ 10.0, C(8′)H), 3.29 (3H, s, OCH_3), 3.01 (1H, dd, $J_{2,3}$ 5.0 $J_{3,3'}$ 12.0, C(3)H), 2.96 (1H, dd, $J_{5,6}$ 7.0 $J_{5,5'}$ 12.0, C(5)H), 2.62 (1H, app. d, $J_{5,5'}$ 12.0, C(5′)H), 2.12 (1H, dd, $J_{2,3'}$ 10.0 $J_{3,3'}$ 12.0, C(3′)H), 0.87 (9H, s, $C(CH_3)_3$); ^{13}C NMR (63 MHz; $CDCl_3$) 138.2 (ArC), 137.7 (ArC), 135.9 (ArC), 130.1 (ArC), 129.7 (ArC), 128.9 (ArC), 128.2 (ArC), 128.0 (ArC), 127.9 (ArC), 102.3 (C7), 72.2 (C2), 69.6 (C6), 65.7 (C8), 63.8 ($PhCH_2N$), 58.9 (C3), 55.5 (OCH_3), 53.8 (C5), 27.1 ($C(CH_3)_3$), 19.5 ($C(CH_3)_3$); *m/z* (CI) 506 (10%, $[M+H]^+$), 218 (12%, $[M-OCH_3-OSi(Ph_2)C(CH_3)_3]^+$), 120 (37%, $[PhCH_2N-CH_2]^+$), found $[M+H]^+$ 506.2713, $C_{30}H_{40}NO_4Si$ requires 506.2727.

Compound **7e**: $[\alpha]_D^{20} = +79.0$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3357 (br s, OH), 2915 (s, CH), 1113 (s, C–O), 1040 (s, C–O); ^1H NMR (250 MHz; $CDCl_3$) 7.76–7.28 (15H, m, Ph), 4.62 (1H, dd, $J_{2,3}$ 9.0 $J_{2,3'}$ 5.0, C(2)H), 4.02–3.97 (1H, m, C(7)H), 3.91–3.89 (3H, m, C(6,8,8′)H), 3.84 (1H, d, *J* 13.5, $PhCH_2N$), 3.74 (1H, d, *J* 13.5, $PhCH_2N$), 3.22 (3H, s, OCH_3), 3.19 (1H, app. d, $J_{5,5'}$ 5.0, C(5)H), 2.94 (1H, dd, $J_{3,3'}$ 14.5 $J_{2,3'}$ 5.0, C(3′)H), 2.59 (1H, dd, $J_{3,3'}$) 14.5 ($J_{2,3}$ 9.0, C(3)H), 2.56–2.54 (1H, m, C(5′)H), 1.10 (9H, s, $C(CH_3)_3$); ^{13}C NMR (63 MHz; $CDCl_3$) 139.1 (ArC), 136.0 (ArC), 135.4 (ArC), 129.90 (ArC), 128.7 (ArC), 128.5 (ArC), 127.9 (ArC), 127.6 (ArC), 100.7 (C2), 72.6 (C6), 71.7 (C7), 67.3 (C8), 63.1 (C5), 61.8 ($PhCH_2N$), 58.8 (C3), 55.8 (OCH_3), 27.2 ($C(CH_3)_3$), 19.6 ($C(CH_3)_3$); *m/z* (CI) 506 (16%, $[M+H]^+$), 274 (14%, $[M-OSi(Ph_2)-C(CH_3)_2]^+$), 218 (43%, $[M-OCH_3-OSi(Ph_2)C(CH_3)_3]^+$), found $[M+H]^+$ 506.2727, $C_{30}H_{40}NO_4Si$ requires 506.2727.

4.14. (2*R*)-[(2*S*,6*S*)-2-(*tert*Butyldiphenylsilanyloxymethyl)-6-methoxy-morpholin-4-yl]-3-phenyl-propionic acid methyl ester 5f and (2*R*)-[(2*S*,6*R*,7*S*)-2-(*tert*butyldiphenylsilanyloxymethyl)-6-hydroxy-7-methoxy-[1,4]-oxazepan-4-yl]-3-phenyl-propionic acid methyl ester 6f

By following the general procedure above, sodium cyanoborohydride (1.6 g, 1.7 mmol) was added to a stirred solution of L-phenylalanine methyl ester (73 mg, 0.34 mmol), the dialdehydes (0.44 g, 1.02 mmol) and 10 Å molecular sieves in methanol (40 mL). Work-up and purification of the residue by flash column chromatography (8:2 Et_2O–hexane) afforded morpholine **5f** (2 mg, 0.0036 mmol, 1%) and [1,4]-oxazepane **6f** (39 mg, 0.068 mmol, 20%) as clear oils.

Compound **5f**: $[\alpha]_D^{20} = +18.8$ (*c* 0.4, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 2926 (s, CH), 2854 (s, CH), 1732 (s, C=O), 1113 (s, C–O), 1058 (s, C–O); ^1H NMR (400 MHz; $CDCl_3$) 7.74–7.18 (15H, m, Ph), 4.71–4.70 (1H, m, C(6)H), 4.17–4.11 (1H, m, C(2)H), 3.70 (1H, dd, $J_{2,7}$ 5.0 $J_{7,7'}$ 11.0, C(7)H), 3.59 (1H, dd, $J_{2,7'}$ 5.0 $J_{7,7'}$ 11.0, C(7′)H), 3.54 (3H, s, OCH_3), 3.49 (1H, dd, *J* 3.0 *J* 11.0, $PhCH_2CH$), 3.41 (3H, s, OCH_3), 3.11 (2H, m, $PhCH_2CH$), 2.99 (1H, dd, $J_{2,3}$ 18.0 $J_{3,3'}$ 12.0, C(3)H), 2.95 (1H, app. d, $J_{5,5'}$ 11.0, C(5)H), 2.61 (1H, dd, $J_{2,3'}$ 2.5 $J_{3,3'}$ 12.0, C(3′)H), 2.29 (1H, app. t, $J_{5',6}$ $J_{5,5'}$ 11.0, C(5′)H), 1.06 (9H, s, $C(CH_3)_3$); ^{13}C NMR (101 MHz; $CDCl_3$) 171.2 (CO), 137.6 (ArC), 136.6 (ArC), 136.2 (ArC), 129.8 (ArC), 129.2 (ArC), 128.8 (ArC), 128.2 (ArC), 127.8 (ArC), 127.1 (ArC), 126.6 (ArC), 97.1 (C6), 69.8 ($PhCH_2CH$), 69.3 (C2), 65.1 (C7), 55.1 (OCH_3), 54.2 (C5), 51.0 (OCH_3), 50.3 (C3), 36.0 ($PhCH_2CH$), 26.8 ($C(CH_3)_3$), 19.2 ($C(CH_3)_3$); *m/z* (EI) 547 (13%, $[M]^+$), 488 (82%, $[M-CO_2CH_3]^+$), 456 (100%, $[M-PhCH_2]^+$), found $[M]^+$ 547.2742, $C_{32}H_{41}NO_5Si$ requires 547.2754.

Compound **6f**: $[\alpha]_D^{20} = +1.7$ (*c* 1.9, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3382 (br s, OH), 2930 (s, CH), 1736 (s, C=O), 1113 (s, C–O), 1069 (s, C–O); ^1H NMR (400 MHz; $CDCl_3$) 7.60–7.54 (5H, m, Ph), 7.36–7.15 (10H, m, Ph), 4.43 (1H, d, $J_{6,7}$ 6.0, C(7)H), 4.12–4.05 (1H, m, C(2)H), 3.95–3.88 (1H, m, C(6)H), 3.68 (3H, s, OCH_3), 3.61 (1H, dd, *J* 10.0 *J* 5.0, $PhCH_2CH$), 3.49 (1H, dd, $J_{2,8}$ 6.0 $J_{8,8'}$ 10.0 C(8)H), 3.39 (1H, dd, $J_{2,8'}$ 6.0 $J_{8,8'}$ 10.0 C(8′)H), 3.35 (3H, s, OCH_3), 3.16 (1H, dd, *J* 14.0 *J* 5.0, $PhCH_2H$), 3.13 (1H, dd, $J_{5,6}$ 7.0 $J_{5,5'}$ 12.5 C(5)H), 2.99 (1H, app. d, $J_{3,3'}$ 12.0 C(3)H), 2.90 (1H, dd, *J* 14.0 *J* 10.0, $PhCH_2CH$), 2.76–2.69 (2H, m, C(5′,3′)H), 1.03 (9H, s, $C(CH_3)_3$); ^{13}C NMR (63 MHz; $CDCl_3$) 172.7 (CO), 137.9 (ArC), 136.8 (ArC), 135.0 (ArC), 129.9 (ArC), 129.3 (ArC), 128.7 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.1 (ArC), 102.1 (C7), 72.5 (C2), 69.9 ($PhCH_2CH$), 69.5 (C6), 65.6 (C8), 58.6 (C3), 56.3 (OCH_3), 52.0 (OCH_3), 51.0 (C5), 36.3 ($PhCH_2CH$), 27.2 ($C(CH_3)_3$), 19.6 ($C(CH_3)_3$); *m/z* (CI) 578 (63%, $[M+H]^+$), 486 (82%, $[M-PhCH_2]^+$), 454 (10%, $[M-OCH_3-PhCH_2]^+$), found $[M+H]^+$ 578.2939, $C_{33}H_{44}NO_6Si$ requires 578.2938.

4.15. General method for entry to [1,4]-oxazepanes 7

4.15.1. Step 1: Synthesis of dialdehyde. A solution of sodium periodate (1.2 equiv) in distilled water was added dropwise to a stirred solution of methyl 4-*O*-benzyl-α-D-glucopyranoside **14** (1 equiv) in methanol at 0 °C and then the reaction mixture stirred at room temperature for 1.5 h. The reaction mixture was concentrated in vacuo and the resulting colourless solid dissolved in ethanol, filtered through Celite® and concentrated in vacuo to yield the crude dialdehyde **14** as a colourless foam.

4.15.2. Step 2: Reductive amination reaction. Sodium cyanoborohydride (5 equiv) was added to a stirred solution of the amine (1 equiv), the dialdehyde (3 equiv) and 10 Å molecular sieves in methanol. After stirring for 24 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was partitioned between H_2O and dichloromethane and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo.

4.16. Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-((2*S*,6*S*,7*R*)-6-benzyloxy-7-hydroxymethyl-2-methoxy-[1,4]-oxazepan-4-yl)-α-D-glucopyranoside 7g

By following the general procedure above, sodium cyanoborohydride (28 mg, 0.45 mmol) was added to a stirred solution of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-amino-α-D-glucopyranoside **10** (45 mg, 0.09 mmol), dialdehyde (84 mg, 0.27 mmol) and 10 Å molecular sieves in methanol (25 mL) and the pH of the reaction mixture adjusted to 7 using HCl (0.20 mL, 2 M soln in Et_2O). Work-up and purification of the residue by flash column chromatography (97:3 CH_2Cl_2–MeOH) afforded **7g** (31 mg, 4.14 mmol, 46%) as a clear oil; $[\alpha]_D^{20} = +53.5$ (*c* 0.2, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3503 (br s, OH), 2924 (s, CH), 1496 (w, C=C), 1070 (s, C–O); ^{1}H NMR (400 MHz; $CDCl_3$) 7.39–7.15 (20H, m, Ph), 5.00 (1H, d, *J* 11.0, $PhCH_2O$), 4.93 (1H, d, *J* 11.0, $PhCH_2O$), 4.81 (1H, d, *J* 10.5, $PhCH_2O$), 4.78 (1H, d, *J* 10.5, $PhCH_2O$), 4.65–4.61 (2H, m, C(2a)H, $PhCH_2O$), 4.51 (1H, d, $J_{1,2}$ 3.5, C(1)H), 4.48 (1H, d, *J* 11.0, $PhCH_2O$), 4.40 (1H, d, *J* 11.0, $PhCH_2O$), 4.14 (1H, d, *J* 11.0, $PhCH_2O$), 3.99 (1H, app. t, $J_{2,3}$ $J_{3,4}$ 9.0, C(3)H), 3.85 (1H, ddd, $J_{4,5}$ 12.0 $J_{5,6}$ 1.0 $J_{5,6'}$ 9.0, C(5)H), 3.80 (3H, m, C(7a,8a,8a′)H), 3.56 (1H, ddd, $J_{5a,6a}$ 5.0 $J_{5a',6a}$ 9.0 $J_{6a,7a}$ 12.0, C(6a)H), 3.45 (1H, dd, $J_{1,2}$ 3.5 $J_{2,3}$ 10.0, C(2)H), 3.38 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.35–3.31 (1H, m, C(4)H), 3.25 (1H, dd, $J_{5a,6a}$ 5.0 $J_{5a,5a'}$ 13.0, C(5a)H), 3.18 (1H, dd, $J_{2a,3a}$ 5.0 $J_{3a,3a'}$ 15.0, C(3a)H), 3.02 (1H, dd, $J_{5,6}$ 1.0 $J_{6,6'}$ 14.0, C(6)H), 2.72 (1H, dd, $J_{5,6'}$ 7.5 $J_{6,6'}$ 14.0, C(6′)H), 2.64–2.59 (2H, m, C(3a′,5a′)H); ^{13}C NMR (101 MHz; $CDCl_3$) 138.7 (ArC), 138.4 (ArC), 138.1 (ArC), 137.9 (ArC), 128.5–127.7 (ArC), 100.5 (C2a), 98.0 (C1), 82.1 (C3), 80.1 (C2), 79.5 (C4), 76.1 (C6a), 75.8 ($PhCH_2O$), 75.1 ($PhCH_2O$), 73.4 ($PhCH_2O$), 72.5 ($PhCH_2O$), 72.0 (C5), 70.1 (C7a), 64.0 (C8a), 60.6 (C5a), 59.6 (C6), 57.0 (C3a), 55.6 (OCH_3, OCH_3); *m/z* (CI) 714 (100%, $[M+H]^+$), 578 (22%, $[M-PhCH_2-OCH_3]^+$), 548 (8%, $[M-PhCH_2-OCH_3-OCH_3]^+$), found: $[M+H]^+$ 714.3643, $C_{42}H_{52}NO_9$ requires $[M+H]^+$ 714.3637.

4.17. ((2*S*,6*S*,7*R*)-4-Benzyl-6-benzyloxy-2-methoxy-[1,4]-oxazepan-7-yl)-methanol 7h

By following the general procedure above, sodium cyanoborohydride (527 mg, 8.35 mmol) was added to a stirred solution of benzylamine (0.18 mL, 1.67 mmol), dialdehyde (1.4 g, 5.01 mmol) and 10 Å molecular sieves in methanol (20 mL). Work-up and purification of the residue by flash column chromatography (2:8 hexane–Et_2O) afforded **7h** as a clear oil (136 mg, 0.38 mmol, 23%); $[\alpha]_D^{20} = +91.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz; $CDCl_3$) 7.29–6.91 (10H, m, Ph), 4.69 (1H, dd, $J_{2,3}$ 13.0 $J_{2,3'}$ 8.0, C(2)H), 4.54 (1H, d, *J* 12.5, $PhCH_2O$), 4.46 (1H, d, *J* 12.5, $PhCH_2O$), 3.95 (1H, ddd, $J_{6,7}$ 13.0 $J_{7,8}$ 9.0 $J_{7,8'}$ 4.0, C(7)H), 3.88–3.79 (4H, m, C(8,8′)H, $PhCH_2N$), 3.60 (1H, ddd, $J_{5,6}$ 9.0 $J_{5',6}$ 5.0 $J_{6,7}$ 13.0, C(6)H), 3.39 (3H, s, OCH_3), 3.28 (1H, dd, $J_{5,5'}$ 5.0 $J_{5,6}$ 9.0, C(5)H), 3.02 (1H, dd, $J_{2,3}$ 13.0 $J_{3,3'}$ 5.0, C(3)H), 2.64–2.50 (2H, m, C(3′,5′)H); ^{13}C NMR (63 MHz; $CDCl_3$) 139.1 (ArC), 138.3 (ArC), 129.1 (ArC), 128.8 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 100.9 (C2), 76.5 (C6), 72.8 (C7), 72.6 ($PhCH_2O$), 64.4 (C8), 61.4 ($PhCH_2N$), 60.4 (C5), 58.4 (C3), 55.9 (OCH_3); *m/z* (CI) 358 (58%, $[M+H]^+$), 328 (14%, $[M-OCH_3]^+$), 266 (13%, $[M-PhCH_2]^+$), found: $[M+H]^+$ 358.2002, $C_{21}H_{28}NO_4$ requires $[M+H]^+$ 358.2018.

4.18. (2*R*)-((2*S*,6*S*,7*R*)-6-Benzyloxy-7-hydroxymethyl-2-methoxy-[1,4]-oxazepan-4-yl)-3-phenyl-propionic acid methyl ester 7i

By following the general procedure above, sodium cyanoborohydride (747 mg, 11.9 mmol) was added to a stirred solution of L-phenylalanine methyl ester (512 mg, 2.37 mmol), dialdehyde (2.22 g, 7.11 mmol) and 10 Å molecular sieves in methanol (100 mL). The reaction mixture was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was partitioned between 1 M HCl (200 mL) and dichloromethane (3200 mL) and the organic phase dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (8:2 Et_2O–hexane) to yield **7i** (545 mg, 1.26 mmol, 53%) as a clear oil; $[\alpha]_D^{20} = +64.3$ (*c* 1.0, $CHCl_3$); ν_{max} (NaCl disc)/cm^{-1} 3479 (br s, OH), 2905 (s, CH), 1732 (s, C=O), 1604 (w, C=C), 1070 (s, C–O); ^{1}H NMR (250 MHz; $CDCl_3$) 7.35–7.18 (10H, m, Ph), 4.63 (1H, dd, $J_{2,3}$ 5.0 $J_{2,3'}$ 3.0, C(2)H), 4.59 (1H, d, *J* 11.5, $PhCH_2O$), 4.53 (1H, d, *J* 11.5, $PhCH_2O$), 3.89 (1H, ddd, $J_{6,7}$ 13.0 $J_{7,8}$ 9.0 $J_{7,8'}$ 3.0, C(7)H), 3.70 (2H, m, C(8,8′)H), 3.64 (3H, s, OCH_3), 3.52 (2H, m, C(6)H, $PhCH_2CH$), 3.39 (3H, s, OCH_3), 3.30 (1H, dd, $J_{5,5'}$ 13.0 $J_{5,6}$ 5.0, C(5)H), 3.11 (1H, dd, $J_{2,3}$ 5.0 $J_{3,3'}$ 15.0, C(3)H), 3.05 (1H, dd, *J* 13.5 *J* 8.0, $PhCH_2CH$), 2.88 (1H, dd, *J* 13.5 *J* 8.0, $PhCH_2CH$), 2.73 (1H, dd, $J_{2,3'}$ 8.0 $J_{3,3'}$ 15.0, C(3′)H), 2.52 (1H, dd, $J_{5,5'}$ 13.0 $J_{5',6}$ 9.0, C(5′)H) ; ^{13}C NMR (63 MHz; $CDCl_3$) 172.9 ($COCH_3$), 138.4 (ArC), 138.2 (ArC), 129.6 (ArC), 129.0 (ArC), 128.8 (ArC), 128.1 (ArC), 127.5 (ArC), 126.9 (Ph), 100.7 (C2), 77.2 (C6), 72.8 ($PhCH_2O$), 72.2 (C7), 70.5 ($PhCH_2CH$), 64.3 (C8), 58.7 (C3), 57.4 (C5), 55.8 (OCH_3), 51.9 (OCH_3),

36.7 (Ph*C*H_2CH); *m*/*z* (CI) 430 (7%, $[M+H]^+$), 338 (18%, $[M-PhCH_2]^+$), 454 (10%, $[M-OCH_3-PhCH_2-PhCH_2]^+$), found $[M+H]^+$ 430.2224, $C_{24}H_{32}NO_6$ requires 430.2230.

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