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# Carbohydrate-derived aminoalcohol ligands for asymmetric Reformatsky reactions

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**Abstract**—Members of a family of functionally and stereochemically diverse D-glucosamine-derived tertiary aminoalcohol ligands have been used to promote the asymmetric Reformatsky reaction. The β-hydroxyester product *tert*-butyl 3-phenyl-3-hydroxy-propanoate was obtained enriched in either the (+)-(*R*) (up to 74% ee) or (−)-(*S*) (up to 42% ee) enantiomer depending on the choice of ligand. Although the selectivities are modest in absolute terms they represent some the better selectivities obtained to date for this reaction. A $^1$H NMR study was conducted to investigate this selectivity and suggested a secondary binding mode between ligand and zinc in addition to the expected N-2, O-3 coordination.


## 1. Introduction

The Reformatsky reaction is one of the most synthetically useful methods for the preparation of β-hydroxyesters.[1] Since the first example of an enantioselective version of the reaction in 1973 using (−)-sparteine,[2] a wide range of chiral ligands, most notably tertiary aminoalcohols **4a**–**d**, has been applied to this reaction using bromoacetate-[3] and difluorobromoacetate[4]-derived Reformatsky reagents **2a**–**c** (Scheme 1). A general, enantioselective method affording β-hydroxyesters **3a**–**c** in high yield and ee, however, remains elusive and selectivities above 70% ee are rare. Compound **4a**-promoted reaction of ethyl bromoacetate-derived Reformatsky reagent **2b** with benzaldehyde in 68% yield and 90% ee has given the most highly enantioenriched products.[3a] The greatest selectivity achieved using *tert*-butyl bromoacetate-derived **2a** was 78% ee (56% yield) and was achieved using ligand **4d**.[3b]

Carbohydrates have recently received much attention as sources of chiral ligands for asymmetric catalysis,[5] however to our knowledge there is only one example[6] of a carbohydrate-derived ligand for the Reformatsky reaction, open chain D-mannitol derived **4e**, which afforded the desired product in 58% yield and only 30% ee. As part of our ongoing studies[7] into the application of glucosamine-derived, aminoalcohol ligands to promote asymmetric transformations we report here results using a small family of carbohydrate tertiary aminoalcohol ligands **4f**–**k**, in the Reformatsky reaction.

## 2. Results and discussion

### 2.1. Preliminary ligand screening and optimisation

We synthesised a family of stereochemically and functionally diverse 1,2-aminoalcohol ligands based on a 4-6-*O*-benzylidene-D-glucosamine scaffold. Based on initial screening of primary and secondary amines and consistent with the nature of the Reformatsky reaction as determined by previous studies,[3a,e] we selected tertiary amine ligands as a preferred motif. Functional diversity was introduced through alkylation of the key, primary amine intermediate **8** by heating with the appropriate alkyl iodides and potassium carbonate in acetonitrile (Scheme 2). Using ethyl iodide, 1,5-diiodopentane and di(2-iodoethyl)ether, acyclic and cyclic tertiary amines **4f**–**h** were prepared in 84–91%, with little or no associated quaternisation.

We used the Reformatsky reaction of benzaldehyde with *tert*-butyl bromoacetate-derived **2a** (Scheme 1) as a standard method to test the effects of changing reaction conditions and ligands. Reformatsky reactions of **2a** have

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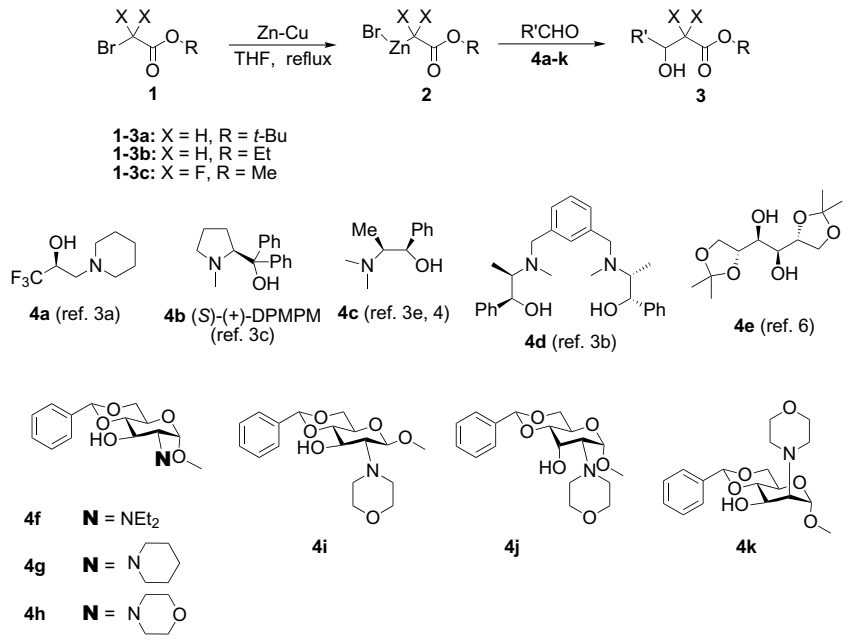
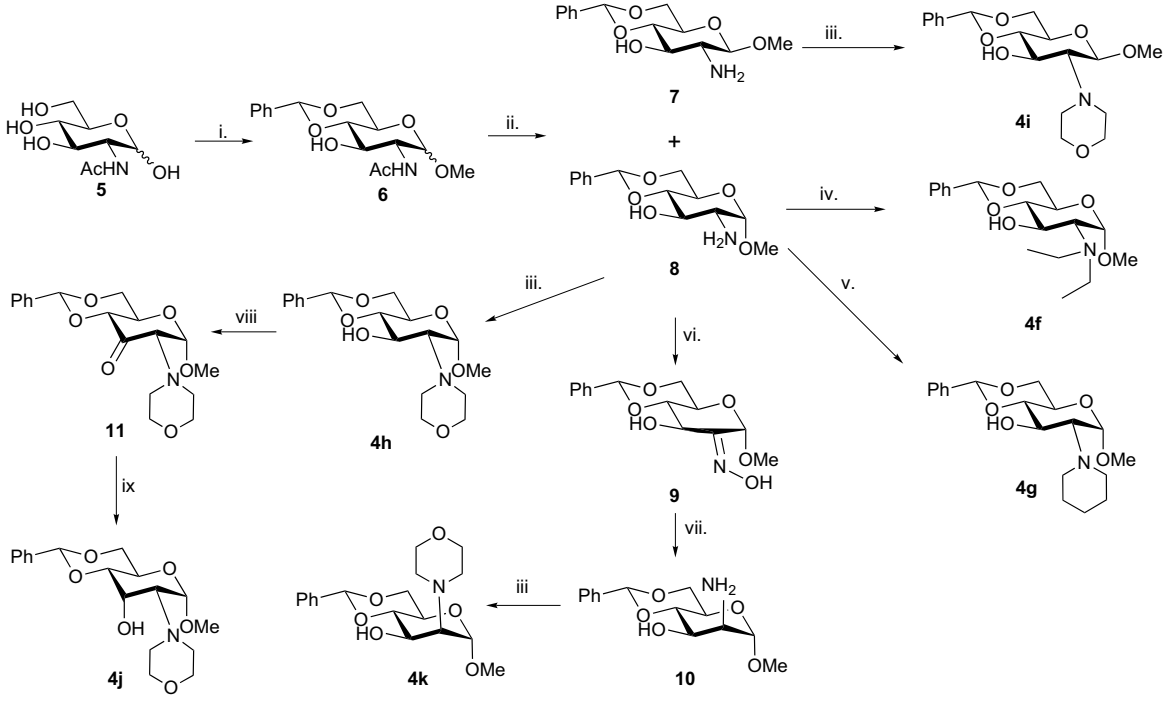



**Scheme 1.**




**Scheme 2.** Reagents and conditions: (i) MeOH, AcCl, 100%, then $PhCH(OMe)_2$, *p*-TsOH, DMF, 70 °C, 69%; (ii) KOH (4 M) EtOH, reflux, 70%, then chromatography; (iii) $I(CH_2)_2O(CH_2)_2I$ (3 equiv), $K_2CO_3$, MeCN, reflux, 91% for **4h**, 66% for **4k**, 74% for **4i**; (iv) EtI (2.1 equiv), $K_2CO_3$, MeCN, reflux, 84%; (v) $I(CH_2)_5I$ (3 equiv), $K_2CO_3$, MeCN, reflux, 85%; (vi) $H_2O_2$, $NaWO_4$, $NaHCO_3$, $H_2O$–MeOH, 46%; (vii) $LiAlH_4$, $H_2SO_4$, THF, 36%; (viii) DMSO, $(COCl)_2$, $Et_3N$, DCM, −78 °C, 82%; (ix) K-Selectride, THF, −78 °C, 62%.

proven to be the most testing both in terms of yield and selectivity and we felt that this would provide the more rigorous trial of our methodology. In this initial screen of α-glucosamine-derived ligands **4f**–**h**, the 2-diethylamino ligand **4f** gave desired β-hydroxyester **3a** in 25% yield and 15% ee; the piperidinyl ligand **4g**, an analogue of **4f** in which the amine alkyl substituents are cyclically constrained, failed to promote the reaction at all; while the 2-morpholinyl ligand **4h** gave the most promising result, a yield of 20% but with better selectivity (42% ee) than **4f** (Table 1).

Based on this lead result we sought to optimise yield and selectivity. Studies using ligand **4h** (Table 1) suggested

**Table 1.** Reformatsky reaction of benzaldehyde with **2a** accelerated by ligands **4f–k**

| Ligand | Temp/°C | Time/h | Ratio; **4**:**2a**[a]: PhCHO | Yield/%[b] **3a** | Ee/%[c] (config.)[d] |
|---|---|---|---|---|---|
| **4f** | 0 | 24 | 1:3:1 | 25 | 15 (*S*) |
| **4g** | 20 | 24 | 1:3:1 | Nil | — |
| **4h** | 0 | 24 | 1:3:1 | 20 | 42 (*S*) |
| **4h** | 20 | 24 | 1:3:1 | 20 | 35 (*S*) |
| **4h** | 20 | 24 | 1:6:1 | 57 | 16 (*S*) |
| **4h** | 0 | 24 | 1:6:1 | 30 | 19 (*S*) |
| **4h** | 0 | 48 | 2:6:1 | 44 | 42 (*S*) |
| **4i** | 20 | 48 | 2:6:1 | 21 | 33 (*S*) |
| **4j** | 20 | 48 | 2:6:1 | 10 | 74 (*R*) |
| **4k** | 20 | 48 | 2:6:1 | Nil | — |

[a] Assuming 100% conversion of bromoacetate **1a** to enolate **2a**.
[b] After isolation by column chromatography.
[c] Ee determined by chiral GC analysis (C-DEX-β).
[d] Configuration determined by sign of specific rotation previously assigned.[22]

that there was a minimal temperature effect; a small decrease in ee occurred (42–35%) when the temperature was changed from 0 to 20 °C. However the ratio of ligand: Reformatsky reagent: aldehyde was more important and the yield was improved from 20% to 57% when a 1:6:1, rather than a 1:3:1 ratio was used, but with a consequent halving of selectivity (ee change from 35% to 16%). The optimal results in combined terms of both ee (42%) and yield (44%) were achieved when a 2:6:1 ratio of ligand: Reformatsky reagent: aldehyde was used.

### 2.2. Effects of ligand stereochemistry

To explore the effects of ligand stereochemistry we next prepared three further diastereomers of α-gluco ligand **4h** arising from inversion of configuration at C-1, C-2 and C-3. The β-gluco ligand, **4i** (C-1 inversion) was prepared from **7** through dialkylation with di(2-iodoethyl)ether in 74% yield, which in turn was isolated by chromatography of an anomeric mixture of **7** and **8**. The ligand with α-allo stereochemistry **4j** (C-3 inversion) was prepared from **4h** via Swern oxidation followed by reduction using K-Selectride in 51% yield over two steps. C-2 epimerisation was performed via an analogous oxidation/selective reduction strategy: primary amine **8** was converted to oxime **9** in 46% yield using sodium tungstate and hydrogen peroxide.[8] Reduction of oxime **9** using $AlH_3$, prepared by reaction of $LiAlH_4$ with $H_2SO_4$,[9] afforded a 58% yield of a 3:2 mixture of the desired primary amine with α-manno configuration **10**, and α-gluco **8**; alkylation of **10** with di(2-iodoethyl)ether gave **4k** in 66%.

These three new diastereomeric ligands **4i–k** were then tested in the Reformatsky reaction, using the previously determined 2:6:1 ratio of ligand: Reformatsky reagent: aldehyde. In all cases a temperature of 20 C was required for reaction. When the β-gluco ligand **4i** was used in the Reformatsky reaction, slightly diminished reactivity and selectivity (21% yield, 33% ee) were observed compared to α-gluco **4h**. The α-manno C-2 epimer **4k** failed to promote the reaction but the α-allo C-3 epimer **4j** showed both a remarkable reversal of the sense of induction ($S \rightarrow R$) as well as much higher selectivity (74% ee); unfortunately the efficiency was greatly reduced (10%).

### 2.3. NMR studies

Although the yields and enantioselectivities obtained were disappointing in absolute terms, they compare reasonably well with other systems and only two examples[3b,c] report enantioselectivities higher than 65% ee for addition of benzaldehyde to *tert*-butyl bromoacetate. In order to obtain a better insight into the mode of binding of the Reformatsky reagent to the ligand and to better understand the role of the ligand, an NMR study was undertaken, using mixtures of the Reformatsky reagent and representative ligand, **4h** in variable ratios. THF-$d_8$ was used as solvent since all reactions were performed in THF.

Reformatsky reagent **2a** was generated and isolated by heating zinc dust and copper(I) chloride in dry THF for half an hour, then adding *tert*-butyl bromoacetate dropwise and heating at reflux for a further hour, before cooling and allowing to settle. A sample of the supernatant liquid was then removed from the reaction and concentrated. Its NMR spectrum in THF-$d_8$ showed expected[10] resonances for methylene ($\delta = 1.81$) and *tert*-butyl protons ($\delta = 1.36$) as well as those for unreacted bromoacetate **1a** ($\delta = 3.75, 1.23$) (Fig. 1).[11]

Next, the $^1$H NMR spectrum of ligand **4h** was recorded in THF-$d_8$, and portions of Reformatsky reagent **2a** were added to the sample. The chemical shifts of the resonances due to H-1, H-2, H-3 and PhC*H* were monitored (Fig. 2), and in all cases steady increases in chemical shift as well as general broadening of peaks were observed as the ratio **2a**:**4h** was increased to 1:1 (Fig. 2). These changes are consistent with binding of zinc by the amino alcohol function at O-3 and N-2 and appear to show the formation of a single species, but may represent several rapidly exchanging, bidentate and monodentate species. These results contrast with the findings of previous NMR studies of the asymmetric Reformatsky reaction in which $^1$H NMR revealed resonances due to several new species in a 1:1 mixture of a less rigid, chiral ligand and Reformatsky reagent.[10] This might therefore reflect a less dynamic nature of the reaction mixture obtained from **4h** with Reformatsky regent **2a**.

Interestingly, when the ratio of Reformatsky reagent to ligand was increased beyond 1:1 to 2:1, a second peak due to PhC*H* was observed at $\delta = 5.65$, while little or no notable change was observed in other peaks. This second distinct shift is suggestive of a second zinc in proximity to the 4,6-oxygen system, and was further supported by an additional signal for *ortho*-Ph benzylidene protons; a new peak emerging at $\delta = 7.65$. When the ratio was increased to 5:1 these two new peaks increased in intensity so that the original peaks ($\delta = 5.58$ (PhC*H*), 7.47 (*ortho*-Ph)) all but disappeared (Fig. 2). Together this is suggestive of a secondary binding mode between the zinc species and the ligand, to give a 'doubly bound'

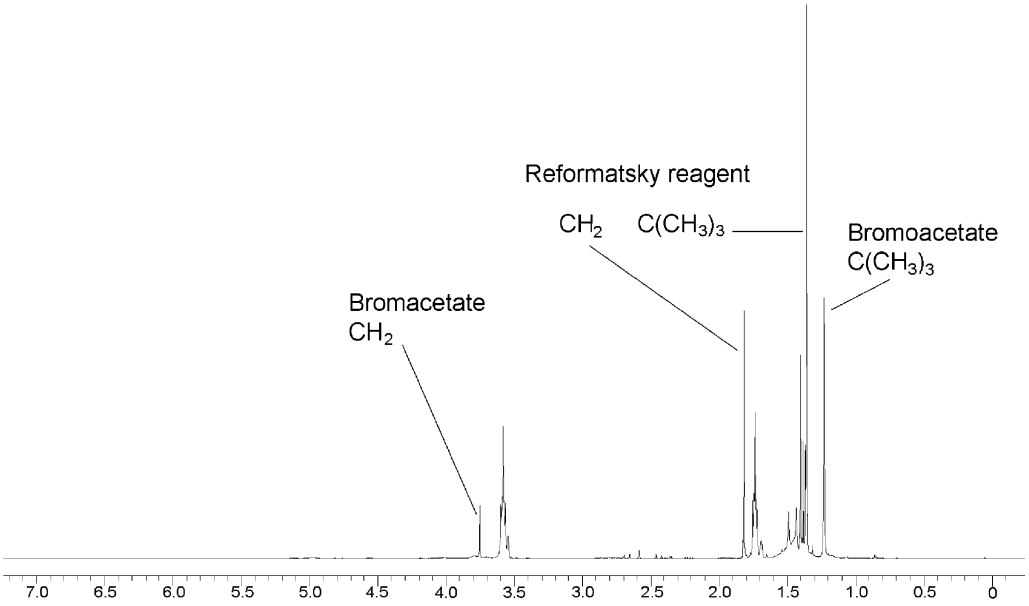



**Figure 1.** [1]H NMR spectrum of Reformatsky reagent, **2a** in THF-$d_8$ at 400 MHz and 293 K.

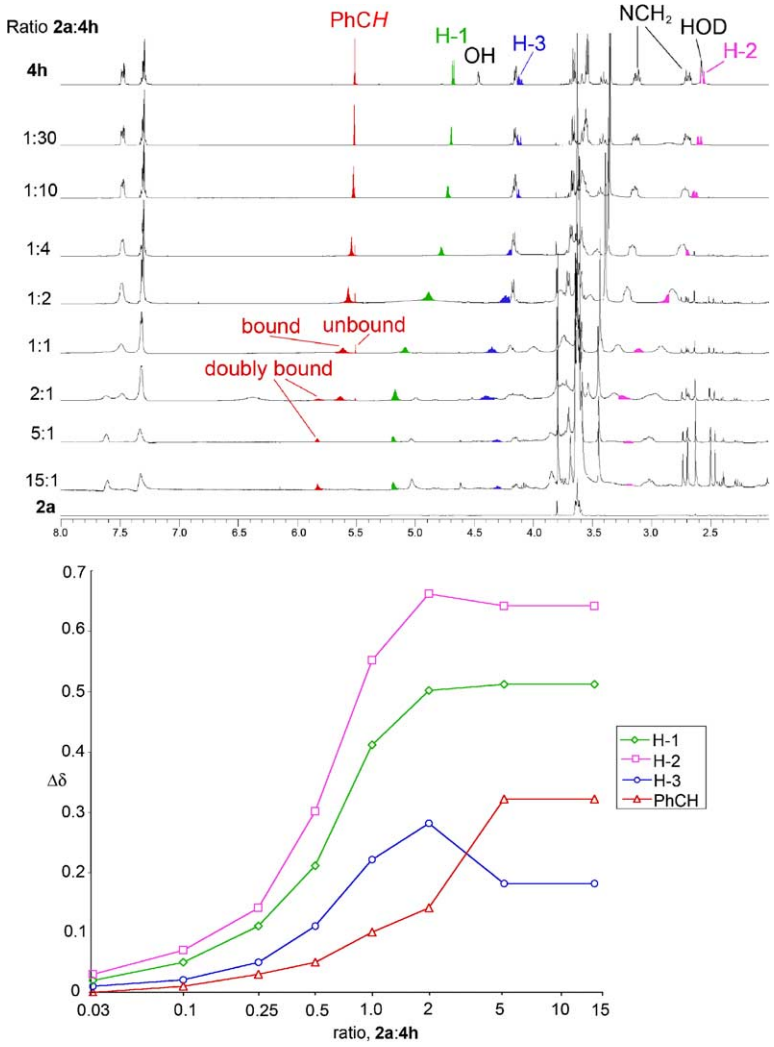



**Figure 2.** Variable-ratio NMR study of ligand **4h** and Reformatsky reagent **2a** in THF-$d_8$ at 400 MHz and 293 K and plot of $\Delta\delta$ versus ratio **2a**:**4h**.

ligand species, the second binding mode possibly being through the oxygen atoms at the 4- and 6-positions of ligand **4h**. These distinct changes in $\delta$ ($\Delta\delta$) are plotted in Figure 2, which highlights this biphasic shift.

The predominant species observed in these $^1$H NMR spectra may not be the reactive one; indeed theoretical studies[12] and crystallographic evidence[13] suggest that although a dimeric species of **2a** predominates in solution, the reactive species is monomeric. It may be that this additional putative O-4, O-6 binding mode between the zinc and ligand is detrimental to the enantioselectivity and reactivity in this reaction. The secondary binding mode that we have observed may be due to the ligand coordinating dimeric Reformatsky reagent in which the second zinc is close to O-4, O-6 and the first held by N-2 and O-3. Indeed, qualitative $^1$H NMR analysis of the nonreactive complex formed between **4k** and **2a** appear to show a higher proportion of shifted and broadened benzylidene peak indicative of this secondary mode. This proposal raises the question of the nature of the Reformatsky reagent when *ligand* is in excess: is it dimeric or monomeric? The lack of a signal due to secondary binding of zinc to the ligand suggests that either it is monomeric or, more likely, that a second ligand coordinates the dimer. Reactions using a 1:1 ratio of ligand **4h**: Reformatsky reagent **2a** in an attempt to reduce this putative secondary binding mode failed to afford any of the desired product.

Although the secondary binding mode by ligand may help to explain the generally low reactivity it cannot account for the differences observed. The remarkable change in the sense selectivity on changing from α-gluco **4h** to α-allo **4i** ($S \rightarrow R$) may be explained by considering that, in the latter case, the zinc is forced bellow the ring, exposing it to steric bulk on one face only, whereas in the case of **4h** the zinc is held more distantly from the sugar ring by the equatorial coordinating 3-OH.

## 3. Conclusions

In conclusion we have demonstrated that fine-tuning of functionality and stereochemistry in D-glucosamine-derived aminoalcohol ligands can give rise to a diverse family of ligands, all members of which may be prepared from a key intermediate in three steps or fewer. The Reformatsky reaction was promoted by these ligands and the resulting β-hydroxyesters were enriched in either enantiomer, depending on the choice of ligand. Some of the selectivities (up to 74% ee for **2a**) are amongst the best seen for the reaction ($\leqslant$78% for **2a**); although efficiencies are generally poor. The ability to access both enantiomers in this way also demonstrates the utility of fine-tuning in ligand design.

We have presented $^1$H NMR evidence suggesting a secondary ligand–zinc binding mode in addition to the expected N,O-coordination of zinc and we have postulated an intermediate in which ligand coordinates dimeric Reformatsky reagent through the 4,6-oxygen system as well as the N-2, O-3 aminoalcohol.

## 4. Experimental methods

### 4.1. General methods

Ether, DCM and THF were distilled; dry toluene, other dry solvents were Fluka 'puriss' solvents. Silica gel (Merck, 400 mesh) was used for column chromatography. TLC was performed on Merck $F_{254}$ silica gel precoated, aluminium backed sheets. Melting points were determined on a Leica Galen III melting point apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 1000 FT-IR spectrometer. NMR spectra were recorded on a Bruker 400 or 200 MHz spectrometer, assignments of peaks are made by means of COSY, HMQC and APT experiments. High resolution mass spectra were measured on Waters 2790 Micromass LCT electrospray ionisation mass spectrometer using chemical ionisation ($NH_3$, Cl). Gas Chromatograms were measured using a β-CD chir-DEX, 25 m column.

### 4.2. Methyl *N*-acetyl-D-glucosamine, 5

*N*-Acetyl-D-glucosamine (36 g, 162.7 mmol) was dissolved in dried methanol (700 mL) and acetyl chloride (57.5 g, 732 mmol) was added slowly. The resulting mixture was stirred for 23 h and the solvent was evaporated affording crude methyl *N*-acetyl-D-glucosamine, in quantitative yield, as a 3/2 α/β anomeric mixture; mp 181 °C (MeOH/AcOEt); {lit.,[14] mp 166 °C; lit.,[15] $mp_{\alpha anom.}$(EtOH) 195 °C; lit.,[16] $mp_{\beta anom.}$-(EtOH) 200 °C}; $[\alpha]_D^{24} = +83$ (*c* 1.0, $H_2O$); {lit.,[17] $[\alpha]_{D\,\beta anom.}^{25} = -46.9$ (*c* 2.0, $H_2O$); lit.,[18] $[\alpha]_{D\,\alpha anom.}^{25} = +127$ (*c* 1.0, $H_2O$)}; $\nu_{max}/cm^{-1}$ (KBr): 3382 (O–H), 2934 (N–H), 1651 (amide I), 1573 (amide II); $\delta_H$ (400 MHz, $CD_3OD$) 4.73 (0.6H, d, *J* 3.5, H-1$_\alpha$), 4.38 (0.4H, d, *J* 8.3, H-1$_\beta$), 3.96 (0.6H, dd, *J* 10.6 and 3.4), 3.90 (0.4H, dd, *J* 12.0 and 1.8), 3.84 (0.6H, *J* 11.9 and 3.8), 3.76–3.69 (2H, m), 3.59–3.45 (1.4H, m), 3.40 (1.2H, s, $CH_3O$), 3.36 (1.8H, s, $CH_3O$), 3.33 (1H m,), 2.23 (1.2H, s, Ac), 2.20 (1.8H, s, Ac); $\delta_C$ (100 MHz, $CD_3OD$) 101.8, 98.12 (2 × C-1), 77.1, 74.6, 72.7, 71.5, 71.1, 70.9, 61.6, 61.5 (2 × C-6), 57.6, 56.2, 55.62, 55.56, 54.5, 48.9 (2 × $OCH_3$), 20.5, 20.3 (2 × $COCH_3$); *m/z* (APCI+) 236.18 ($[M+H]^+$), (APCI−) 234.37 ($[M-H]^+$).

### 4.3. Methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside, 6

Methyl *N*-acetyl-D-glucosamine, (162.7 mmol) was dissolved in DMF (400 mL); benzaldehyde dimethyl acetal (48.8 mL, 325.4 mmol) and *para*-toluenesulfonic acid (0.62 g, 3.25 mmol) were added and the mixture stirred at 70 °C for 2.5 h. The product was identified by mass spectrometry (*m/z* (APCI+) 324.27, $[M+H]^+$) and the solvent was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (1.0 L) and saturated sodium hydrogen carbonate solution (500 mL). Undissolved material was removed by filtration, dissolved in hot chloroform (700 mL) and recrystallised to give methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside. The organic layer from the partition was separated, washed with brine (100 mL),

dried over $MgSO_4$ and evaporated, recrystallisation from ethyl acetate (700 mL) gave methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (total yield, 36 g, 69%, overall anomeric ratio, 4/1, α/β).

**4.3.1. Methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside.** White solid; $R_f$ 0.4 (9/1, $CHCl_3$/MeOH); mp 298 °C (EtOAc); $[\alpha]_D^{24} = +90$ (*c* 0.11, MeOH); $\nu_{max}/cm^{-1}$ (KBr) 3436 (OH), 3294 (NH), 3090 (CH, aromatic) 2990, 2946, 2912, 2872, 2834 (CH, aliphatic), 1653 (amide I), 1555 (amide II); $\delta_H$ (400 MHz, $CDCl_3$) 7.52–7.35 (5H, m, Ph), 5.93 (1H, d, *J* 8.6, NH), 5.57 (1H, s, C*H*Ph), 4.73 (1H, d, *J* 3.8, H-1), 4.29 (1H, dd, *J* 3.2 and 8.3, H-6), 4.23 (1H, ddd, *J* 3.8, 8.9 and 10.2, H-2), 3.91 (1H, t, *J* 9.5, H-3), 3.83–3.75 (2H, m, H-5, H-6′), 3.59 (1H, m, H-4), 3.41 (3H, s, $OCH_3$), 3.24 (1H, s, OH), 2.06 (3H, s, Ac); $\delta_C$ (100 MHz, $CDCl_3$) 171.5 ($CH_3CO$), 137.0, 129.2, 128.3, 126.3 (Ph), 102.0 (*C*HPh), 98.8 (C-1), 82.0 (C-4), 70.7 (C-3), 68.8 (C-6), 62.3 (C-5), 55.3 ($OCH_3$), 54.0 (C-2), 23.3 ($CH_3CO$); *m*/*z* (TOF, ES+) 324.1447 ($[M+H]^+$, $C_{16}H_{22}NO_6$ requires 324.1442).

**4.3.2. Methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside.** White solid; $R_f$ 0.3 (9/1, $CHCl_3$/MeOH); mp 292 °C (MeOH); $[\alpha]_D^{24} = -57$ (*c* 0.21, MeOH) {lit.[19] $[\alpha]_D^{25} = -59.3$ (*c* 0.56, MeOH)}; $\delta_H$ (400 MHz, $CDCl_3$) 7.45 (2H, m, Ph), 7.23 (3H, m, Ph), 6.08 (1H, d, *J* 6.5, NH), 5.53 (1H, s, C*H*Ph), 4.57 (1H, d, *J* 8.9, H-1), 4.27 (1H, dd, *J* 3.5 and 10.4, H-6), 4.25 (1H, ddd, *J* 6.5, 8.9 and 9.8, H-2), 4.06 (1H, pt, *J* 9.4, H-4), 3.91 (1H, pt, *J* 9.6, H-3), 3.83–3.75 (2H, m, H-5, H-6′), 3.60–3.54 (1H, m, OH), 3.50 (3H, s, OMe), 2.04 (3H, s, $C(O)CH_3$); $\delta_C$ (100 MHz, $CD_3OD$) 171.5 ($CH_3CO$), 137.0, 129.1, 128.3, 126.3 (4 × Ph), 102.0 (PhCH), 101.7 (C-1), 81.6 (C-4), 71.3 (C-3), 68.0 (C-6), 58.5 (C-5), 57.0 (OMe), 54.1 (C-2), 23.6 ($CH_3CO$).

### 4.4. Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside, 7/8

Methyl 2-*N*-acetylamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (31.84 g, 99 mmol) was added to 4 M KOH in ethanol (800 mL) and heated at reflux for 4 h. TLC (9/1 $HCCl_3$/MeOH) showed completion and the reaction was concentrated to 600 mL and diluted with DCM (1 L). This mixture was washed twice with water (2 × 1.5 L), dried ($MgSO_4$) and concentrated under reduced pressure to give crude product as an orange solid (23.1 g). Column chromatography (9/1–5/1 $CHCl_3$/MeOH) allowed separation of the anomers, affording methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside as a white solid (19.5 g, 70%).

**4.4.1. Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside, 8.** $[\alpha]_D^{25} = +103.1$ (*c* 0.905, $CHCl_3$); mp (MeOH/EtOAc) 135 °C (dec), 172 °C (melt); $\nu_{max}/cm^{-1}$ (KBr) 3376, 3300 (OH, $NH_2$), 3068, 3036 (CH, aromatic), 2993, 2966, 2872, 2835 (CH, aliphatic), 1576, 1455 (CC, aromatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.50–7.36 (5H, m, Ph), 5.52 (1H, s, CHPh), 4.65 (1H, d, *J* 3.5, H-1), 4.26 (1H, dd, *J* 9.3 and 4.0, H-6), 3.82–3.70 (2H, m, H-4, H-6′), 3.65 (1H, pt, *J* 9.1, H-3), 3.43 (1H, pt, *J* 9.3, H-5), 3.39 (3H, s, $OCH_3$), 2.74 (1H, dd, *J* 9.6 and 3.5, H-2); $\delta_C$ (50 MHz, $CDCl_3$) 137.3, 129.2, 128.3, 126.4, (4 × Ph), 101.9 (*C*HPh), 101.2 (C-1), 82.1 (C-5), 76.0 (C-3), 69.1 (C-6), 62.6 (C-4), 56.6 (C-2), 55.4 ($OCH_3$); *m*/*z* (TOF, ES+) 282.1350 ($[M+H]^+$, $C_{14}H_{20}NO_6$ requires 282.1341).

**4.4.2. Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside, 7.** $[\alpha]_D^{25} = -55.6$ (*c* 0.90, $CHCl_3$); mp (MeOH/EtOAc): 159.5–160.5 °C; $\nu_{max}/cm^{-1}$ (KBr) 3435 ($NH_2$), 3174 (OH), 2938, 2879 (CH, aliphatic), 1600, (CC, aromatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.48–7.31 (5H, m, Ph), 5.51 (1H, s, C*H*Ph), 4.31 (1H, dd, *J* 10.4 and 4.9, H-6), 4.15 (1H, d, *J* 7.94, H-1), 3.76 (1H, pt, *J* 10.4, H-6′), 3.56 (1H, pt, *J* 9.1, H-3), 3.49 (1H, pt, *J* 9.0, H-4), 3.48 (3H, s, $OCH_3$), 3.35–3.42 (1H, m, H-5), 2.75 (1H, dd, *J* 8.4 and 8.5, H-2); $\delta_C$ (50 MHz, $CDCl_3$) 137.2, 129.3, 128.4, 126.3 (4 × Ph), 105.3 (C-1), 102.0 (*C*HPh), 81.5 (C-4), 72.8 (C-3), 68.7 (C-6), 66.5 (C-5), 57.8 (C-2), 57.4 ($OCH_3$); *m*/*z* (TOF, ES+) 282.1351 ($[M+H]^+$, $C_{14}H_{20}NO_6$ requires 282.1341).

### 4.5. Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*,*N*-diethylamino-α-D-glucopyranoside, 4f

Ethyl iodide (120 μL, 2.1 mmol), potassium carbonate (206 mg, 1.50 mmol) and **8** (200 mg, 0.78 mmol) were added to acetonitrile and heated at 60 °C for a total of 60 h, further portions of ethyl iodide were added after 10 h (85 μL, 1.07 mmol), 22 h (58 μL, 0.71 mmol), 30 h (58 μL) and 54 h (29 μL, 0.34 mmol). The reaction was filtered, concentrated under reduced pressure and purification by column chromatography (0–10% MeOH/EtOAc) afforded **4f** (201 mg, 84%) as a colourless syrup; $R_f$ 0.4 (10% MeOH/EtOAc); $[\alpha]_D^{24} = +113$ (*c* 1.23, $CHCl_3$); (found: C 63.65, H 8.4, N 4.1. $C_{18}H_{27}NO_5$ requires C 64.1, H 8.1, N 4.15%); $\nu_{max}/cm^{-1}$ ($CHCl_3$) 3431br (OH), 2969, 2928, 2858 (CH, aliphatic), 1459w (CC, aromatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.54–7.51 (2H, m, Ph), 7.38–7.33 (3H, m, Ph), 5.59 (1H, s, C*H*Ph), 4.83 (1H, d, *J* 2.5, H-1), 4.27 (1H, dd, *J* 9.8 and 4.5, H-6), 4.08 (1H, dd, *J* 10.5 and 8.8, H-3), 3.85 (1H, ddd, *J* 10.4, 9.2 and 4.5, H-5), 3.77 (1H, pt, *J* 10.1, H-6′), 3.61 (1H, pt, *J* 9.0, H-4), 3.47 (1H, s, OH), 3.38 (3H, s, $OCH_3$), 2.90 (2H, dq, *J* 13.7 and 7.4, $NCH_2$), 2.84 (1H, dd, *J* 10.5 and 3.0, H-2), 2.62 (2H, dq, *J* 13.7 and 7.0, $NCH_2$), 1.06 (3H, pt, *J* 7.6, $CH_2CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 137.3, 129.0, 128.2, 126.4 (Ph), 101.7 (*C*HPh), 99.2 (C-1), 83.3 (C-4), 69.1 (C-6), 65.4 (C-3), 64.8 (C-2), 62.2 (C-5), 55.9 ($OCH_3$), 44.4 ($NCH_2$), 14.8 ($CH_2CH_3$); *m*/*z* (TOF, ES+) 338.1974 ($[M+H]^+$, $C_{18}H_{28}NO_5$ requires 338.1967).

### 4.6. Methyl 4-6-*O*-benzylidene-2-deoxy-2-(1-piperidinyl)-α-D-glucopyranoside, 4g

1,5-Diiodopentane (116 μL, 0.78 mmol), potassium carbonate (108 mg, 0.78 mmol) and **8** (200 mg, 0.78 mmol) were added to acetonitrile and the reaction was heated

at 60 °C for 12 h, then at 78 °C for 8 h. A further portion of 1,5-diiodopentane (53 μL) was then added and the reaction was heated at reflux for 15 h. The reaction was filtered, concentrated under reduced pressure and purification by column chromatography (2.5–15% MeOH/DCM) afforded **4g** (210 mg, 85%) as an amorphous, white solid; $R_f$ 0.4 (10% MeOH/EtOAc); $[\alpha]_D^{24} = +106$ (*c* 1.63, $CHCl_3$) (found: C 65.00, H 7.70, N 4.00. $C_{19}H_{27}NO_5$ requires C 65.30, H 7.80, N 4.00%); $\nu_{max}/cm^{-1}$ (KBr) 3454br (OH), 2929, 2852 (CH, aliphatic), 1455 (CC, aromatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.53–7.51 (2H, m, Ph), 7.38–7.33 (3H, m, Ph), 5.58 (1H, s, C*H*Ph), 4.85 (1H, d, *J* 3.0, H-1), 4.26 (1H, dd, *J* 9.6 and 4.3, H-6), 4.13 (1H, dd, *J* 10.6 and 8.8, H-3), 3.84 (1H, ddd, *J* 10.3, 9.1 and 4.4, H-5), 3.77 (1H, pt, *J* 10.0, H-6′), 3.59 (1H, pt, *J* 9.0, H-4), 3.39 (3H, s, $OCH_3$), 2.83–2.78 (2H, m, $NCH_2$), 2.67 (1H, dd, *J* 10.6 and 3.0, H-2), 2.67–2.63 (2H, m, $NCH_2$), 1.63–1.46 (6H, m, $NCH_2CH_2$, $NCH_2CH_2CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 137.3, 129.0, 128.1, 126.4 (Ph), 101.7 (*C*HPh), 98.8 (C-1), 83.4 (C-4), 69.4 (C-2), 69.1 (C-6), 64.8 (C-3), 62.3 (C-5), 54.6 ($OCH_3$), 51.0 ($NCH_2$), 27.0 ($NCH_2CH_2$), 24.7 ($NCH_2CH_2CH_2$); *m*/*z* (TOF, ES+) 350.1971 ($[M+H]^+$, $C_{19}H_{28}NO_5$ requires 350.1967).

### 4.7. Methyl 4-6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-glucopyranoside, 4h

Di(2-iodoethyl)ether[20] (255 mg, 0.78 mmol), potassium carbonate (108 mg, 0.78 mmol) and **8** (200 mg, 0.78 mmol) were added to acetonitrile and heated at 70 °C for 24 h a further portion of di(2-iodoethyl)ether (70 mg) was then added and the reaction was heated at reflux for 6 h. Removal of solvent under reduced pressure and purification by column chromatography (2.5–5% MeOH/DCM) afforded **4h** (226 mg, 0.64 mmol, 91%) as a white solid; $R_f$ 0.4 (5% MeOH/$CHCl_3$); mp 155–157.5 °C (DCM); $[\alpha]_D^{24} = +92$ (*c* 1.97, $CHCl_3$); (found: C 61.50, H 7.20, N 4.00. $C_{18}H_{25}NO_6$ requires C 61.50, H 7.15, N 4.00%); $\nu_{max}/cm^{-1}$ (KBr) 3440 (OH), 3067w (CH, aromatic), 2975, 2928, 2863 (CH, aliphatic), 1458 (CC, aromatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.52–7.49 (2H, m, Ph), 7.39–7.34 (3H, m, Ph), 5.57 (1H, s, C*H*Ph), 4.85 (1H, d, *J* 3.1, H-1), 4.27 (1H, dd, *J* 9.6 and 4.2, H-6), 4.18 (1H, dd, *J* 10.3 and 9.1, H-3), 3.83 (1H, ddd, *J* 10.3, 9.0 and 4.3, H-5), 3.76 (1H, pt, *J* 9.6, H-6′), 3.71 (2H, ddd, *J* 11.1, 5.7 and 3.4, $CH_2O$), 3.66 (2H, ddd, *J* 11.1, 5.7 and 3.4, $CH_2O$), 3.57 (1H, pt, *J* 9.1, H-4), 3.40 (3H, s, $OCH_3$), 3.15 (1H, s, OH), 2.84 (4H, m, $CH_2N$), 2.70 (1H, dd, *J* 10.6 and 3.1, H-2); $\delta_H$ (400 MHz, THF-$d_8$) 7.48–7.46 (2H, m, Ph), 7.32–7.28 (3H, m, Ph), 5.51 (1H, s, C*H*Ph), 4.67 (1H, d, *J* 3.8, H-1), 4.46 (1H, d, *J* 3.1, OH), 4.16–4.09 (2H, m, H-3, H-6), 3.66–3.64 (2H, m, H-5, H-6), 3.54 (4H, pt, *J* 4.7×, $OCH_2$), 3.41 (1H, m, H-4), 3.34 (3H, s, $OCH_3$), 3.12 (2H, m, $NCH_2$), 2.69 (2H, m, $NCH_2$), 2.57 (1H, dd, *J* 10.6, 3.4, H-2); $\delta_C$ (100 MHz, $CDCl_3$) 137.2, 129.1, 128.2, 126.3 (4 × Ph), 101.8 (PhCH), 99.3 (C-1), 83.2 (C-4), 69.1 (C-6), 68.6 (C-2), 67.8 ($CH_2O$), 65.4 (C-3), 62.2 (C-5), 54.7 ($OCH_3$), 50.3 ($CH_2N$); *m*/*z* (TOF, ES+) 352.1772 ($[M+H]^+$, $C_{18}H_{26}NO_6$ requires 352.1760).

### 4.8. Methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranoside-2-ulose *Z*-oxime, 9

Hydrogen peroxide (35% (aq v/v), 1.38 mL, 7.12 mmol) was added dropwise to a solution of 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside **8** (200 mg, 0.71 mmol), sodium tungstate dihydrate (23.8 mg, 0.071 mmol) and sodium hydrogen carbonate (72 mg, 0.86 mmol) in methanol/water (1:1, 10 mL). The reaction was stirred at room temperature for 34 h during which time further portions of methanol (total 10 m) were added to partially dissolve the precipitate that formed. TLC (10% MeOH/EtOAc) indicated completion and the methanol was evaporated under reduced pressure. Water was added to the aqueous residue and this was extracted three times with ethyl acetate; the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (5–15% MeOH/DCM) afforded methyl 4,6-*O*-benzylidene-α-D-*arabino*-hexopyranoside-2-ulose *Z*-oxime (97 mg, 46%) as a white solid; $R_f$ 0.7 (10% MeOH/EtOAc); mp 140 °C, crystal form change, 196–197 °C, melts; $[\alpha]_D^{24} = +40$ (*c* 1.16, $CHCl_3$); $\nu_{max}/cm^{-1}$ (KBr) 3510, 3392br (OH), 2973, 2947, 2920, 2878 (CH aliphatic), 1642 (C=N); $\delta_H$ (400 MHz, DMSO-$d_6$) 11.39 (1H, s, N–OH), 7.54–7.43 (2H, m, Ph), 7.40–7.37 (3H, m, Ph), 5.77 (1H, s, H-1), 5.64 (1H, s, PhC*H*), 5.31 (1H, d, *J* 6.1, OH), 4.35 (1H, dd, *J* 9.7 and 5.9, H-3), 4.23 (1H, dd, *J* 8.8 and 3.8, H-6), 3.78 (1H, ptd, *J* 9.9 and 4.5, H-5), 3.74 (1H, pt, *J* 10.4, H-6′), 3.59 (1H, pt, *J* 9.5, H-4), 3.36 (3H, s, $OCH_3$); $\delta_C$ (100 MHz, DMSO-$d_6$) 152.9 (C-2), 138.5, 129.8, 128.9, 127.2 (Ph), 101.5 (*C*HPh), 92.7 (C-1), 83.2 (C-4), 69.1 (C-3), 68.6 (C-6), 63.7 (C-5), 55.7 ($OCH_3$); *m*/*z* (TOF, ES−) 294.0970 ($[M-H]^-$, $C_{14}H_{16}NO_6$ requires 294.0978). The oxime was assigned as the *Z*-isomer on the basis of a strong NOE enhancement between H-1 and NOH but not between H-3 or C-3-OH and NOH.

### 4.9. Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside, 10[21]

$H_2SO_4$ (concd, 91 μL) was added dropwise, with vigorous stirring, over 5 min to $LiAlH_4$ (1 N, THF, 3.39 mL) in THF (1.7 mL) in a two-necked flask equipped with a reflux condenser and cooled in a water bath. After 1 h stirring at room temperature, **9** (100 mg, 0.34 mmol) was added dropwise as a solution in THF (2 mL) over 10 min. TLC indicated completion after 5 h whereupon the reaction was quenched by the dropwise addition of water, and $NaHCO_3$. The solvents were evaporated under reduced pressure and the residue taken up in methanol and filtered over Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography affording methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside, **8** (27 mg, 22%) and methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside, **10** (35 mg, 36%) as a white solid; $R_f$ 0.1 (5% MeOH/$CHCl_3$); mp 102–105 °C; $[\alpha]_D^{24} = +26$ (*c* 1.24, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3414 (O–H), 2931 (C–H aliphatic); $\delta_H$ (400 MHz, $CDCl_3$)

7.52–7.49 (2H, m, Ph), 7.39–7.35 (3H, m, Ph), 5.57 (1H, s, C*H*Ph), 4.66 (1H, s, H-1), 4.27 (1H, dd, *J* 8.5 and 3.2, H-6), 4.03 (1H, dd, *J* 9.7 and 4.7, H-3) 3.82–3.77 (2H, m, H-5, H-6′), 3.69 (1H, pt, *J* 9.3, H-4), 3.38 (3H, s, $OCH_3$), 3.28 (1H, d, *J* 4.5, H-2); $\delta_C$ (100 MHz, $CDCl_3$) 137.3, 129.2, 128.3, 126.3 (4 × Ph), 103.3 (C-1), 102.3 (*C*HPh), 79.6 (C-4), 68.9 (C-6), 67.5 (C-3), 62.9 (C-5), 55.0 ($OCH_3$), 54.4 (C-2); *m*/*z* (TOF, ES+) 282.1347 ($[M+H]^+$, $C_{14}H_{20}NO_5$ requires 282.1341).

### 4.10. Methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-mannopyranoside, 4k

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-2-α-D-mannopyranoside (188 mg, 0.67 mmol) and potassium carbonate (102 mg, 0.74 mmol) were dissolved in acetonitrile (50 mL) and di(2-iodoethyl)ether (306 mg, 0.94 mmol) was added; the reaction was heated at reflux for 56 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give **4k** (155 mg, 66%) as a white solid; $R_f$ 0.43 (1:1 petrol/ethyl acetate); mp 168–170 °C (EtOAc); $[\alpha]_D^{24} = -3.8$ (*c* 0.95, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3316 (O–H), 2972, 2906, 2836 (C–H, aliphatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.53–7.51 (2H, m, Ph), 7.38–7.34 (3H, m, Ph), 5.60 (1H, s, PhC*H*), 4.91 (1H, s, H-1), 4.27 (1H, dd, *J* 9.6 and 4.2, H-6), 4.04 (1H, dd, *J* 9.8 and 6.9, H-3), 3.82 (1H, ptd, *J* 9.3 and 4.4, H-5), 3.77–3.69 (5H, m, $OCH_2$, H-6′), 3.67 (1H, pt, *J* 9.5, H-4), 3.38 (3H, s, $OCH_3$), 3.00 (1H, d, *J* 6.8, H-2), 2.92 (2H, ddd, *J* 11.2, 6.2 and 3.1, $NCH_2$), 2.67 (2H, ddd, *J* 11.5, 5.9 and 3.1, $NCH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 137.2 (s, Ph), 129.1, 128.2, 126.3 (3 × d, Ph), 102.1 (*C*HPh), 97.2 (C-1), 81.1 (d, C-4), 69.0 (t, C-6), 67.3 (t, $OCH_2$), 66.8 (d, C-2), 66.0 (d, C-3), 62.2 (d, C-5), 54.7 (q, $OCH_3$), 52.2 (t, $NCH_2$); *m*/*z* (TOF, ES+) 352.1753 ($[M+H]^+$, $C_{18}H_{26}NO_6$ requires 352.1760).

### 4.11. Methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-*ribo*-hexopyranoside-3-ulose, 11

Oxalyl chloride (249 μL, 2.85 mmol) and DMSO (405 μL, 5.70 mmol) were added to DCM (8 mL) at −78 °C and the reaction was stirred for 45 min. A solution of **4h** (0.5 g, 1.42 mmol) in DCM (2 mL) was then added dropwise via syringe. After 2 h triethylamine (2.00 mL, 14.2 mmol) was added and the reaction was allowed to reach room temperature. After a further 2 h brine was added, followed by a few drops of water; the layers were separated and the aqueous layer extracted three times with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure; purification of the resulting residue by column chromatography (gradient: neat ethyl acetate → 5% methanol/ethyl acetate) afforded methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-*ribo*-hexopyranoside-3-ulose **11** (405 mg, 82%) as a white solid; mp 148–155 °C crystal form change, 162–163, melts (EtOAc); $[\alpha]_D^{23} = +105$ (*c* 0.88, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3058, 3032 (C–H aromatic), 2979, 2955, 2927, 2913, 2861, 2833 (C–H aliphatic), 1737 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 7.56–7.50 (2H, m, Ph), 7.37–7.36 (3H, m, Ph), 5.56 (1H, s, C*H*Ph), 5.25 (1H, d, *J* 3.8, H-1), 4.40 (1H, dd, *J* 10.3 and 4.6, H-6), 4.24 (1H, d, *J* 10.3, H-4), 4.09 (1H, ptd, *J* 9.9 and 4.6, H-5), 3.92 (1H, pt, *J* 10.2, H-6′), 3.76 (4H, m, $OCH_2$), 3.44 (3H, s, $OCH_3$), 3.42 (1H, d, *J* 4.0, H-2), 2.89 (2H, m, $NCH_2$), 2.74 (2H, m, $NCH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 196.4 (s, C-3), 136.4 (s, Ph), 129.3, 128.3, 126.4 (3 × d, Ph), 102.4 (d, C-1), 101.9 (d, *C*HPh), 82.6 (d, C-4), 73.3 (d, C-2), 69.5 (t, C-6), 67.1 (t, $OCH_2$), 65.7 (d, C-5), 55.0 (q, $OCH_3$), 50.1 (t, $NCH_2$); *m*/*z* (TOF, ES+) 350.1611 ($[M+H]^+$, $C_{18}H_{24}NO_6$ requires 350.1604).

### 4.12. Methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-allopyranoside, 4j

Methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-*ribo*-hexopyranoside-3-ulose **11** (520 mg, 1.49 mmol) was dissolved in THF and cooled to −78 °C. K-Selectride, (3.6 mL, 1 M, THF) was added and the reaction stirred for 8 h. The reaction was quenched with water and diluted with ethyl acetate, the aqueous layer was extracted with ethyl acetate and the combined organic layers was washed with NaOH (1 M) and brine, then dried ($MgSO_4$) and purified by column chromatography (EtOAc → 20% MeOH/EtOAc) to give **4j** (320 mg, 62%) as a white solid; $R_f$ 0.15 (EtOAc); mp 134–136 °C (EtOAc); $[\alpha]_D^{24} = +59$ (*c* 1.02, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3484 (O–H), 2927, 2856 (C–H aliphatic); $\delta_H$ (400 MHz, $CDCl_3$) 7.53–7.50 (2H, m, Ph), 7.38–7.33 (3H, m, Ph), 5.59 (1H, s, PhC*H*), 4.87 (1H, d, *J* 3.3, H-1), 4.40 (1H, br s, H-3), 4.38 (1H, dd, *J* 10.2 and 5.1, H-6), 4.21 (1H, ptd, *J* 10.0 and 5.1, H-5), 3.79 (4H, pt, *J* 4.7, $OCH_2$), 3.76 (1H, pt, *J* 10.4, H-6′), 3.50 (1H, dd, *J* 9.7 and 2.6, H-4), 3.43 (3H, s, $OCH_3$), 3.21 (1H, s, OH), 2.73 (2H, m, $NCH_2$), 2.53 (2H, m, $NCH_2$), 2.38 (1H, pt, *J* 3.1, H-2); $\delta_C$ (100 MHz, $CDCl_3$) 139 (s, Ph), 129.1, 128.2, 126.3 (3 × d, Ph), 102.1 (d, *C*HPh), 98.4 (d, H-1), 79.6 (d, C-4), 69.2 (t, C-6), 66.7 (t, $OCH_2$), 65.8 (d, C-2), 64.6 (d, C-3), 57.8 (d, C-5), 55.4 (q, $OCH_2$), 50.4 (t, $NCH_2$); *m*/*z* (TOF, ES+) 352.1759 ($[M+H]^+$, $C_{18}H_{26}NO_6$ requires 352.1760).

### 4.13. Methyl 4-6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-β-D-glucopyranoside, 4i

Di(2-iodoethyl)ether (255 mg, 0.78 mmol), potassium carbonate (108 mg, 0.78 mmol) and **7** (200 mg, 0.78 mmol) were added to acetonitrile and heated at 70 °C for 24 h; a further portion of di(2-iodoethyl)ether (70 mg) was added after 24 h. Purification by column chromatography (1–4% MeOH/DCM) afforded **4i** (188 mg, 75%) as a white solid; $R_f$ 0.6 (5% MeOH/$CHCl_3$); mp 148–150 °C (DCM); $[\alpha]_D^{24} = -24$ (*c* 1.73, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.52–7.50 (2H, m, Ph), 7.39–7.34 (3H, m, Ph), 5.57 (2H, s, C*H*Ph), 4.54 (1H, d, *J* 8.5, H-1), 4.33 (1H, dd, *J* 10.4 and 4.9, H-6), 3.82 (1H, pt, *J* 10.2, H-6′), 3.76 (1H, dd, *J* 10.1 and 9.0, H-3), 3.72, 3.67 (4H, 2 × ddd, *J* 8.0, 6.3 and 2.9, $CH_2O$), 3.61 (1H, pt, *J* 9.0, H-4), 3.56 (3H, s, $OCH_3$), 3.40 (1H, ddd, *J* 10.1, 9.3 and 5.0, H-5), 3.06 (2H, br m, $CH_2N$), 2.63 (2H, ddd, *J* 11.3, 6.1 and 3.2, $CH_2N$), 2.43 (1H, dd, *J* 10.2 and 8.5, H-2); $\delta_C$ (100 MHz, $CDCl_3$) 137.1, 129.1, 128.2, 126.3 (4 × Ph), 102.5 (C-1), 101.6 (*C*HPh), 81.5 (C-4), 70.3 (C-2), 68.7 (C-6), 67.74

($CH_2O$), 67.71 (C-3), 66.7 (C-5), 56.6 ($OCH_3$), 50.2 (br, $CH_2N$); $\nu_{max}/cm^{-1}$ (KBr) 3460 (OH), 3032w (CH, aromatic), 2994, 2968, 2907, 2874, 2814 (CH, aliphatic), 1471, 1455 (CC, aromatic); *m/z* (TOF, ES+) 352.1760 ($[M+H]^+$, $C_{18}H_{26}NO_6$ requires 352.1760).

### 4.14. Reformatsky reactions

**4.14.1. Preparation of Reformatsky reagent.** A flame dried two-necked flask fitted with a reflux condenser and septum was charged with zinc dust (392 mg, 6 mmol), CuCl (59.4 mg, 0.6 mmol) and THF (6 mL), then heated to reflux with stirring under nitrogen for 30 min. The flask was then removed from the heat and *tert*-butyl bromoacetate (969 μL, 6 mmol) was added via syringe at such a rate as to maintain gentle reflux. Heating was then resumed for 1 h. Stirring was then stopped and the suspension allowed to settle leaving a green solution of the Reformatsky reagent, $R_f$ 0.7 (3:1 40–60 petroleum spirit/ether).

**4.14.2. Reformatsky reaction, representative procedure.** The ligand **4h** (210 mg, 0.6 mmol) was dissolved in THF (1.25 mL) and stirred under nitrogen at 0 °C. A solution of the Reformatsky reagent (1.8 mL, 1.8 mmol) was added by syringe and stirred for 5 min. Benzaldehyde (30.3 μL, 0.3 mmol) was then added in one portion and the reaction was stirred for 48 h. The reaction was quenched by the addition of saturated, aqueous $NH_4Cl$ (2 mL) and extracted three times with ethyl acetate; the combined organic layers were then washed with saturated sodium bicarbonate solution and brine, and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue purified by column chromatography (gradient: 4:1, petroleum sprit (40–60 °C): ether → neat ether; then 4:1, ethyl acetate: methanol) affording (*S*)-(−)-*tert*-butyl 3-hydroxy-3-phenylpropanoate (29 mg, 44%) as a colourless oil; $[\alpha]_D^{23} = -10.5$ (*c* 2.4, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3454 (O–H), 2979 (C–H, aliphatic), 1728 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ph), 5.09 (1H, dd, *J* 8.3 and 4.4, C*H*OH), 3.48 (1H, br s, OH), 2.67 (2H, m, $CH_2$), 1.46 (9H, s, $C(CH_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.9 (C=O), 142.6, 128.4, 127.6, 125.7 (4 × Ph), 81.5 ($C(CH_3)_3$), 70.4 (CHOH), 44.2 ($CH_2$), 28.1 ($CH_3$); and recovered ligand (199 mg, 95%) as a white solid.

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