Precise structure activity relationships in asymmetric catalysis using carbohydrate scaffolds to allow ready fine tuning: dialkylzinc–aldehyde additions †

Daniel P. G. Emmerson,[a] **Renaud Villard,**[a] **Claudia Mugnaini,**[a] **Andrei Batsanov,**[b] **Judith A. K. Howard,**[b] **William P. Hems,**[c] **Robert P. Tooze**[c] **and Benjamin G. Davis ***[a]

[a] *Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: Ben.Davis@chem.ox.ac.uk; Fax: +44 (0) 1865 275674; Tel: +44 (0) 1865 275652*
[b] *Chemical Crystallography, University of Durham, South Road, Durham, UK DH1 3LE*
[c] *Johnson Matthey Catalysis and Chiral Technologies, 28 Cambridge Science Park, Milton Road, Cambridge, UK CB4 0FP*

The ready construction of 24 stereochemically and functionally diverse carbohydrate ligand structures from a core D-glucosamine scaffold has allowed the evaluation of broad ranging structure activity relationships in ligand accelerated zincate additions to aldehydes, with variations in $\Delta\Delta G^{\ddagger}(R\text{-}S)$ of up to 5650 J mol^{-1} that create opposing senses of asymmetric induction and that are consistent with models based on several ligand X-ray structures and molecular mechanics analysis. Factorial analysis of enantioselectivity using key dihedral angles and steric volume on *N*-2 also highlight the potential for the use of factorial design in ligand construction.

Introduction

Carbohydrates are powerful sources of chirality for use in synthetic asymmetric processes[1] and often prove to be superior to more simple sources.[2] Despite such clear indications, to the best of our knowledge, systematic structure–function relationships of carbohydrate ligands, reagents or catalysts have been rarely[3] explored and instead have typically been limited simply to those that are readily or commercially-available. This seems all the more remarkable given that they are a prime source of contiguous, stereogenic centres that may be readily manipulated both in configuration and functionality to allow rapid fine tuning of their function.[4] We present here, to the best of our knowledge, the most extensive such structure–activity relationship (SAR) study to date.

N-Acetyl-D-glucosamine **1** was chosen as a chiral pool scaffold system and converted into the conformationally rigid 4,6-*O*-benzylidine derivatives **2**–**7**. We reasoned that such a *trans*-decalin-like system would allow us to present the N-2, O-3 aminoalcohol functionality with well-defined dihedral angles and thereby allow clearer interpretation of both the alteration of this geometry and of neighbouring groups within this well-defined chiral pocket. Moreover, we speculated that the rigidity of this system would allow the relaying of the effects of more remote stereogenic centres to those involved in direct metal binding. In this way "second sphere" effects may be transmitted to inner "first sphere" as an example of chiral relay[5] *e.g.*, the configuration of the potentially stereogenic N-2 may be tuned by changing the configuration at C-1 perhaps through steric interaction of the O-1 and N-2 substituents. For this reason conditions were used that allowed the formation of both anomers of **2** and hence gave access to anomeric (α and β) families of ligands, **4** and **5**. In addition ready configurational inversions gave access to third and fourth diastereomeric families **6** and **7**.

The ligand-accelerated addition of dialkylzincs to aldehydes is an exemplar in asymmetric induction. Since the pioneering work of Oguni and Omi,[6] and Noyori and co-workers[7] many classes of ligands *e.g.*, chiral aminoalcohols[8] or sulfonamido-alcohols[9] including isolated examples of unrelated carbohydrate ligands,[10] have been developed and access to addition products in ee's > 95% are now routinely possible.[11] This well-defined system therefore seemed an ideal model within which to validate broad-ranging carbohydrate-ligand tuning.

Results and discussion

In these preliminary studies we report four new diastereomeric families of hexosamine aminoalcohol ligands for the catalysis of the addition of diethylzinc to aldehydes. Amidoalcohol **2** was taken as the starting point from which to derive detailed SARs between ligands by altering the configuration of both directly coordinating centres C-2 and C-3 (1st sphere sites) and neighbouring non-coordinating centre C-1 (2nd sphere site) and *N*-functionalization to generate 24 related ligands **4**–**7**, **a**–**l**.

To achieve this goal we have developed ready methods for interconversion of these ligands using no more than 3 steps (Scheme 1). Initially, a methyl substituent was installed at the anomeric centre of **1** followed by modification of the 4 and 6 positions as a benzylidene to give the desired *trans*-decalin type system, **2**; the flexibility of this route is such that both anomers may be separated at this stage or the combined mixture processed to **4**, **5**. *N*-Acetyl deprotection either with N_2H_2 under sealed tube conditions[12] (for small scale) or through reflux in ethanolic KOH (for larger scale) gave the ligands **4**, **5a** which again were separable by crystallization. A simple alkylation strategy proved suitable for preparation of many of the ligands **b**–**e**, **j**, **h**, **i** but did not allow controlled *N*-benzylation to create **f**, **g**, resulting instead in quarternization or *O*-benzylation. After evaluation of a number of derivatization and/or protection strategies *N*-benzylation **a**→**f** or **g** was achieved using TMSCl;[13] the number of equivalents of TMSCl used determined the clean formation of either mono- (**f** using 2 eq.) or di-benzylated (**g** using 1 eq.) products. It should be noted that this robust route is amenable to scale-up *e.g.*, **2**, **4a** + **5a** and **4g** + **5g**, were prepared on a >50 g scale in 71, 60 and 37% (yielding 18% **4g**,

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.
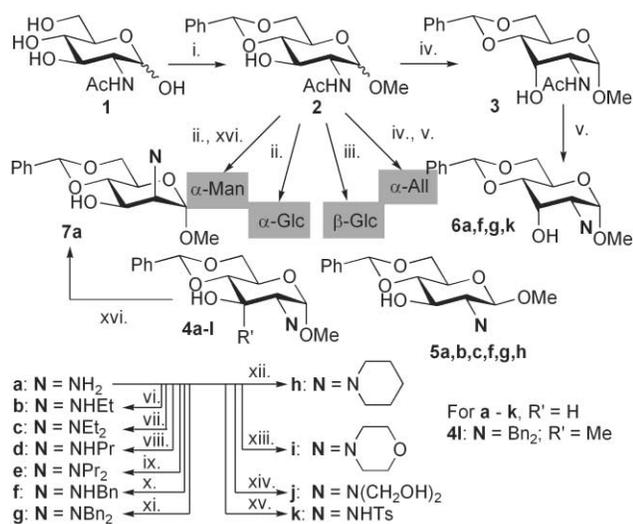
Scheme 1 *Reagents and conditions*: (i) MeOH, AcCl, 100% then PhCH(OMe)$_2$, *p*TsOH, DMF, 70 °C, 69%; (ii) (iii) N$_2$H$_2$, 130 °C, 88%, or 4 M KOH, EtOH, −70–85%; (iv) DMSO, (CF$_3$CO)$_2$O, Et$_3$N, DCM, −78 °C, 75% then L-selectride, THF, −78 °C, 75 then 60% **2→3**, 52 then 74% **4b→6b**, 80 then 60% **4c→6c**; (v) 4 M KOH, EtOH, Δ, 49%; (vi) 1.1 eq. EtI, K$_2$CO$_3$, MeCN, 60 °C, 56% for **4a → 4b**, 42% for **5a → 5b**; (vii) 2.1 eq. EtI, K$_2$CO$_3$, MeCN, 60 °C, 84% for **4a → 4c**, 80% for **5a → 5c**; (viii) 1.1 eq. PrI, K$_2$CO$_3$, MeCN, reflux, 63% for **4a → 4d**; (ix) 3 eq. PrI, K$_2$CO$_3$, MeCN, reflux, 72% for **4a → 4e**, 42% for **5a → 5b**; (x) 2 eq. TMSCl, DIPEA, DCM then BnBr, Bu$_4$NI then Bu$_4$NF, THF, 56% for **4b**, 61% for **5b**; (xi) 1 eq. TMSCl, DIPEA, DCM then BnBr, Bu$_4$NI then Bu$_4$NF, THF, 68% for **4c**, 75% for **5c**; (xii) 1.1 eq. I(CH$_2$)$_5$I, K$_2$CO$_3$, MeCN, 60 °C, 85% for **4a → 4h**, 90% for **5a → 5h**; (xiii) 1.1 eq. I(CH$_2$)$_2$O(CH$_2$)$_2$I, K$_2$CO$_3$, MeCN, 70 °C, 91% for **4a → 4i**, 75% for **5a → 5i**; (xiv) 3 eq. I(CH$_2$)$_2$OH, K$_2$CO$_3$, MeCN, reflux, 39% for **4a → 4j**; (xv) TsCl, Et$_3$N, DCM, 75% for **4d**, 60% for **6d**; (xvi) H$_2$O$_2$, Na$_2$WO$_4$, MeOH–H$_2$O, 46% then LiAlH$_4$, THF, 0→50 °C, 28% for **7a**.

15% **5g**) overall yields from **1**, respectively through routes that utilise no chromatography and only 1–2 crystallization purification steps. For rapid fine tuning, the ligands **6a**, **f**, **g**, **k** were prepared *via* a highly stereoselective oxidation‡–reduction strategy. This robust inversion allowed parallel configurational inversions of α-gluco-**2**→α-allo-**3**, **4f→6f**, **4g→6g** in yields over 2 steps of 38–48%. Finally, a strategically analogous oxidation–reduction process also allowed the ready formation of α-manno-amine **7a** from α-gluco-amine **4a**. Notably, this involved a rarely employed C–N→C=N→C–N transformation that utilizes a modification of the tungstate-mediated oxidation method of Kahr and Berther[14] to form an intermediate *Z*-oxime followed by hydride reduction. This allowed rapid two-step inversion of configuration at C-2 albeit in only moderate yield and poor stereoselectivity in the reduction of oxime to amine **7a**.

The 24 ligands were initially screened in the addition of diethylzinc to benzaldehyde **8** (Table 1). While no high selectivities were observed (**4i** gave the largest ee, 65% (*S*)), due to the systematic nature of our approach fine-tuning of ee allowed SARs to be constructed. From these epimerically variant ligand sets some clear underlying trends could be dissected.

Firstly, enantioselectivity varied according to the ligand stereochemical family in the order **4>5>6>7**. The effects of the anomeric configuration, a 2nd sphere effect, as probed by C-1 epimerisation, α-gluco→β-gluco, **4→5** caused changes in ΔΔG‡ for the transition states that lead to **11R** *vs*. **11S** (ΔΔΔG‡ (*R–S*)) of ~300–2100 J mol^{-1}. These were less pronounced for those ligands with secondary amines at C-2 (ΔΔΔG‡ (*R–S*) <~800 J mol^{-1} for NHR) than those with tertiary amines ((ΔΔΔG‡ (*R–S*) ~1100–2100 J mol^{-1} for NR$_2$) and this may reflect a different mode of asymmetric induction (*vide infra*).

‡ Unsurprisingly, metal-based oxidants failed; screening identified Swern oxidation.

First sphere effects, as probed by C-3 epimerisation, α-gluco→-α-allo, **4→6**, were slightly greater: changes in ΔΔG‡ (*R–S*) were typically ~500 J mol^{-1} larger than 2nd sphere effects in the same ligand system (*e.g.* N = NBn$_2$, **6g→4g** ΔΔΔG‡ (*R–S*) ~1800 J mol^{-1} *cf*. ΔΔΔG‡ (*R–S*) **5g→4g** ~1300 J mol^{-1}). The lowest overall ees from **6** likely reflect α-face metal coordination further from β-face sugar chirality.

Secondly, having established the generally higher *S* enantioselectivity of **4** as a ligand family, we systematically varied the amine on C-2 focussing largely on **4** but also including relevant comparisons with **5** and **6**. Further trends emerged: the presence of a secondary amine group at C-2 (N = NHEt, NHPr, NHBn) as compared to a tertiary amine caused a consistent and significant reduction in ΔΔG‡ (*R–S*) in the range ΔΔΔG‡ (*R–S*) ~−300 to −4600 J mol^{-1} that indeed in 4 cases (**4c→4b**, **5c→5b**, **4e→4d**, **4g→4f**) caused striking reversals in *S* to *R* enantioselectivity (*e.g.* **4e→4d**, 56% *S*→30% *R*). The very different behaviours of N = NHR and N = NR$_2$ ligands again suggests two different modes of induction (*vide infra*).

Thirdly, increasing the size of the amine substituents on N-2 allowed us to probe the effect of interactions around this key Lewis basic site. The N = NR$_2$ subfamily of ligand family **4** provides a useful illustration of trends that were also seen in **5** and **6**. Alteration of the substituent R, N = NEt$_2$(**4c**, 53% *S*)→NPr$_2$(**4e**, 56% *S*)→NBn$_2$(**4g**, 38% *S*) showed a gradual alteration of the selectivity with the size of R that peaked around NPr$_2$. In an attempt to further enhance enantioselectivity, **4h**, **4i** were constructed as "tied-back", cyclically-constrained variants intermediate in size between NEt$_2$ and NPr$_2$. Enantioselectivities were thus increased slightly to 58% *S* and 65% *S*, respectively. A rough ligand-ability order of **i > h> e > c >g** therefore emerged.

We were pleased to obtain X-ray crystal analysis of 3 of the ligands as a valuable additional source of structural information, including ligand **4f** which had generated an unusual reversal (35% *R*) in the sense of induction for **8→11**. These structures revealed (Fig. 1) the predicted, common *trans*-decalin structural motif and that the interaction of the anomeric substituent with the N-2 substituent serves to modulate the location of steric bulk above or below the ring *i.e.*, comparison of **4g** with **5g** shows that, as hoped, the effect of 2nd-sphere epimerisation at C-1 is indeed transmitted to the 1st-sphere and the resulting conformational readjustment around N-2 causes a twist in the disposition of the two Bn groups of the NBn$_2$ that is modulated by the C-1 OMe in a manner akin to a twig in the spokes of a bicycle wheel. From these we have tentatively formulated the model shown in Fig. 1, which invokes a classical Noyori dinuclear intermediate.[15] In this model the C-1 substituent effectively "levers" the Bn or alkyl group on N-2 to control the occupation of the site normally occupied by the Ph of **8** or the appropriate aldehyde. Further support for this model was gained in several ways: (i) The importance of nitrogen coordination was confirmed by the formation of sulfonamides **4,6k**. The lower efficiency of ligands **4,6k** reflected a poor rate of reaction that may be attributed to their poor Lewis basicity; (ii) The key role played by Zn^{2+} coordination in the mechanism was probed by the pre-addition of 20 mol% BuLi (conditions D) and we tested its effect upon the **4a**,**g**-catalysed addition to **8**. The effect of Li$^+$ on zincate additions has been noted previously[16] and in both **4,6g** a significant reduction in enantioselectivity was observed. Indeed, a further unusual reversal in the sense of induction was observed[17] for **4a**; (iii) ligand **4l**,[18] in which the axial H-3 of **4g** is replaced by a Me group, was designed in an attempt to disrupt the putative Zn-binding site shown in Fig. 1 and hence test the model. Consistent with disruption of the binuclear complex **4l** gave greatly reduced enantioselectivity (6%, **11R**); (iv) ligand **4j**, in which two additional potentially coordinating hydroxyl groups were introduced to provide a competing site for Zn complexation also gave a significantly lower ee (12% *R*); (v) initial results of

Table 1 Product enantiomeric excesses, configurations and yields for the reaction of diethylzinc with benzaldehyde **8**→**11**, *p*-chlorobenzaldehyde **9**→**12** and *p*-CF₃-benzaldehyde **10**→**13** in the presence of ligands **4**–**7**

8: X = H
9: X = Cl
10: X = CF₃

11: X = H
12: X = Cl
13: X = CF₃
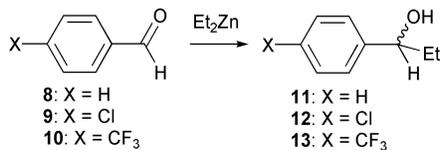
Conditions[a]		Time/h	Yield (%)	8→11 ee (%)[b]	Yield (%)	9→12 ee (%)[b]	Yield (%)	10→13 ee (%)[b]
4a	A	17	66	63*S*	77	49*S*	81	50*S*
4a	B	28	76	32*S*	—	—	—	—
4a	C	28	81	38*S*	—	—	—	—
4a	D	28	86	12*R*	—	—	—	—
4b	A	26	68	20*R*	—	—	—	—
4c	A	26	91	53*S*	—	—	—	—
4d	A	26	92	30*R*	—	—	—	—
4e	A	26	96	56*S*	65	25*S*	88	52*S*
4f	A	23	64	35*R*	—	—	—	—
4g	A	26	77	38*S*	—	—	—	—
4g	D	28	79	20*S*	—	—	—	—
4h	A	26	90	58*S*	85	47*S*	91	55*S*
4i	A	26	86	65*S*	85	62*S*	93	64*S*
4j	A	26	64	12*R*	—	—	—	—
4k	A	28	55	19*S*	—	—	—	—
4l	A	26	63	6*R*	—	—	—	—
5a	A	17	68	46*S*	—	—	—	—
5b	A	26	85	17*R*	—	—	—	—
5c	A	26	93	26*S*	—	—	—	—
5f	A	26	79	14*S*	—	—	—	—
5g	A	26	79	32*S*	—	—	—	—
5h	A	26	77	28*S*	—	—	—	—
5i	A	26	69	28*S*	—	—	—	—
6a	A	28	94	32*S*	—	—	—	—
6f	A	28	96	23*S*	—	—	—	—
6g	A	28	95	0	—	—	—	—
6k	A	28	16	1*R*	—	—	—	—
7a	A	26	88	21*S*	—	—	—	—

[a] Conditions A: 10 mol% ligand, toluene, RT; B: 5 mol% ligand; C: 2.5 mol% ligand; D: 20 mol% BuLi added to ligand at 0 °C, then as for A.
[b] Ee determined by chiral GC analysis (C-DEX-β); configuration by polarimetry.
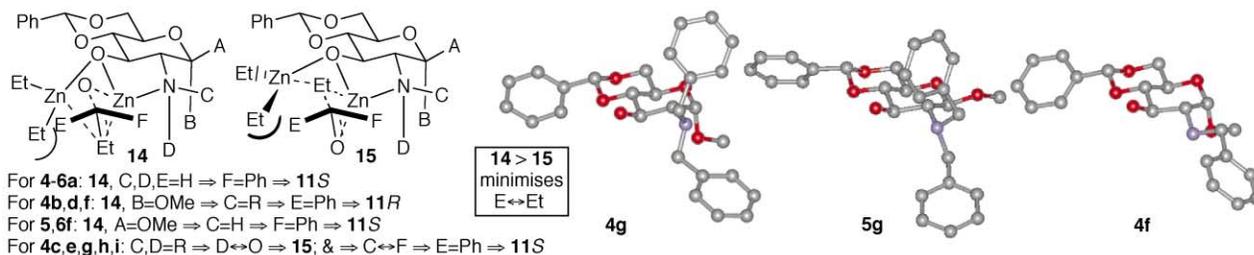

For **4-6a**: **14**, C,D,E=H ⇒ F=Ph ⇒ **11***S*
For **4b,d,f**: **14**, B=OMe ⇒ C=R ⇒ E=Ph ⇒ **11***R*
For **5,6f**: **14**, A=OMe ⇒ C=H ⇒ F=Ph ⇒ **11***S*
For **4c,e,g,h,i**: C,D=R ⇒ D↔O ⇒ **15**; & ⇒ C↔F ⇒ E=Ph ⇒ **11***S*

14 > 15 minimises E↔Et

4g   **5g**   **4f**

Fig. 1 Proposed model consistent with mode of asymmetric addition **8**→**11** and corresponding X-ray structures.§ of **4g**,**5g**,**4f**.

reactions using varying stoichiometries of Et₂Zn–ligand support an optimal ratio consistent with the proposed 2 : 1 stoichiometry. Further experiments investigating non-linear and substrate electronic effects[19] are underway and will be presented in due course.

These empirical, qualitative observations of variations in enantioselectivity were examined in greater quantitative detail through the use of molecular mechanics analysis. This allowed the determination of minimised ligand structures and in combination with the structural information provided by the X-ray structures shown in Fig. 1 allowed corresponding structural parameters to be gathered. These numerical parameters valuably allowed factorial analysis of some of the underlying parameters that determine ee with a view to factorial design.[20] In particular, the rigid scaffold provided by the *trans*-decalin like ligand structures **4**–**7** allowed variation of key dihedral angles with little variation in the supporting scaffold structure. Dihedral angles, O1–C1–C2–N2 (Figs 2,4); N2–C2–C3–O3 (Fig. 2a); O3–C3–C4–O4 (Fig. 2b), ω–N2–C2–C3 (Figs 3,4) as well as steric volume on N-2 (Fig. 3), through the use of Taft parameters[21] were all examined. These highlight trends that indicate first sphere dihedral angles N2–C2–C3–O3 and ω–N2–C2–C3 are the most important. For the latter a clear trend emerges from the factorial analysis: (*R*) stereoselectivity is
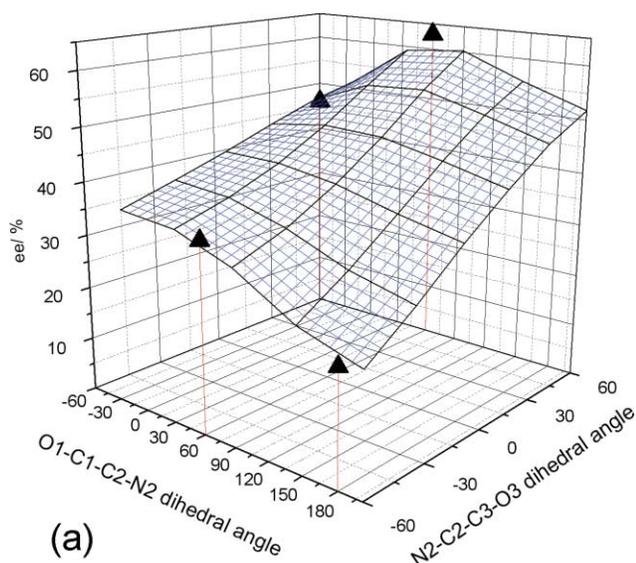
(a)
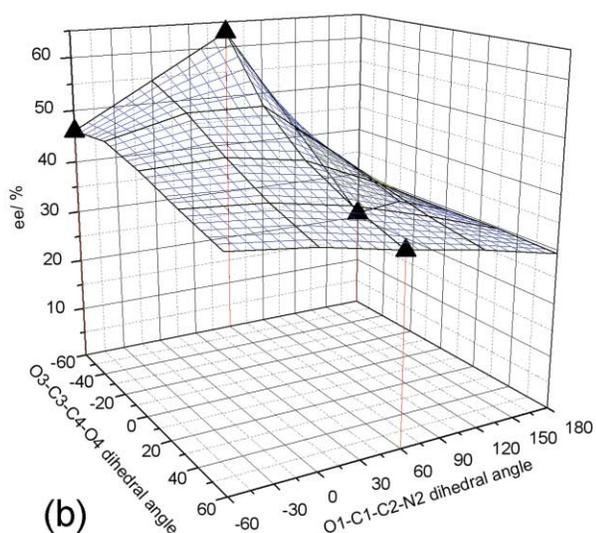
(b)

Fig. 2 Enantioselectivity surface graphs for the primary amine ligands, **4a**, **5a**, **6a** and **7a**. (a) O1–C1–C2–N2 dihedral angle *vs.* N2–C2–C3–O3 dihedral angle. (b) O1–C1–C2–N2 dihedral angle *vs.* O3–C3–C4–O4 dihedral angle. These plots indicate the effect of changing the configuration at the C1, C2 and C3 positions; the importance of the N2–C2–C3–O3 dihedral angle is apparent since the gradient of the surface parallel to the N2–C2–C3–O3-axis is greater than that parallel to the O1–C1–C2–N2-axis. The α-gluco stereochemistry is thus confirmed as the optimum ligand configuration within these 4 ligand diastereomers.

favoured by dihedral angles in the range 80–90°, whilst the more common (*S*) stereoselectivity is found when the dihedral angle is negative (*i.e.* the lone pair is directed above the plane of the sugar ring). When the dihedral angle is in the range 40–45° very low enantioselectivity is observed. This preliminary analysis appears to support not only the chiral relay "twig in a bicycle wheel" effect proposed above but also the potential of factorial analysis in ligand design, which to the best of our knowledge has not been previously utilized.[20] It also highlights future potential ligand targets in which, for example, cyclic constraint in the *N*-substituents might be used to optimise the ω–N2–C2–C3 dihedral angle for (*R*) (+80–90°) or (*S*) (<0°) stereoselectivity and the need for further factorial design. This work is underway and will be presented in due course.

Having examined the addition of Et$_2$Zn to benzaldehyde we next turned to alternative substrates *p*-chlorobenzaldehyde **9** and *p*-trifluoromethylbenzaldehyde **10**. Generally lower levels of induction were observed for **9→12** and **10→13**. However, consistent with the model delineated for **8→11**, enantioselectivities varying with the nature of the C-2 amine in the
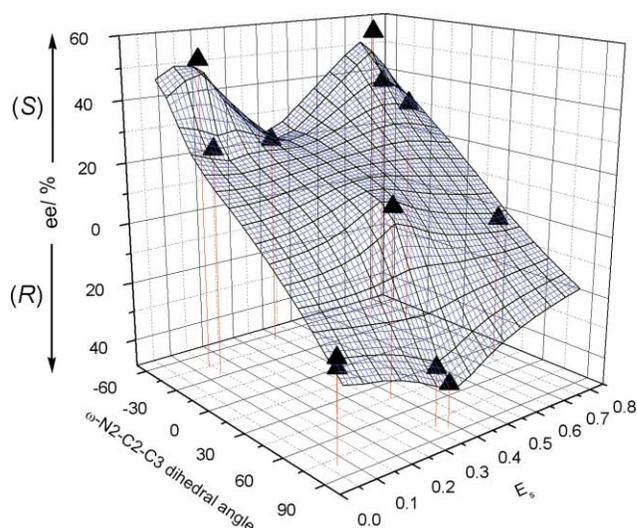

Fig. 3 Enantioselectivity surface graph for the ω–N2–C2–C3 dihedral angle *vs.* *N*-steric bulk as judged by Taft's steric parameter, E_s. *N*-alkyl and *N*-benzyl substituted ligands and corresponding dihedral angles taken from X-ray structures and molecular modeling calculations are shown. **4b** ω–N2–C2–C3 dihedral angle = 80.9°, O1–C1–C2–N2 dihedral angle = 53.4°, E_s = 0.07; **4c** −44.5°, 60.3°, 0.14; **4d** 80.9°, 53.4°, 0.36; **4e** −49.9°, 59.4°, 0.72; **4f** 85.4°, 51.9°, 0.38; **4g** −51.1°, 61.3°, 0.76; **5b** 80.8°, −66.5°, 0.07; **5c** −33.3°, −59.0°, 0.14; **5f** 45.0°, −56.9°, 0.38; **5g** −28.6°, −58.9°, 0.76; **6f** − 52.3°, 42.6°, 0.38; **6g** 41.1°, 57.6°, 0.76. A moderate increase in selectivity with the steric parameter is observed over this range. Far more striking is the relationship between calculated ω–N2–C2–C3 dihedral angle and selectivity. (*R*) stereoselectivity is favoured by dihedral angles in the range 80–90°, whilst the more common (*S*) stereoselectivity is found when the dihedral angle is negative (*i.e.* the lone pair is above the plane of the sugar ring). When the dihedral angle is in the range 40–45° very low enantioselectivity is observed.
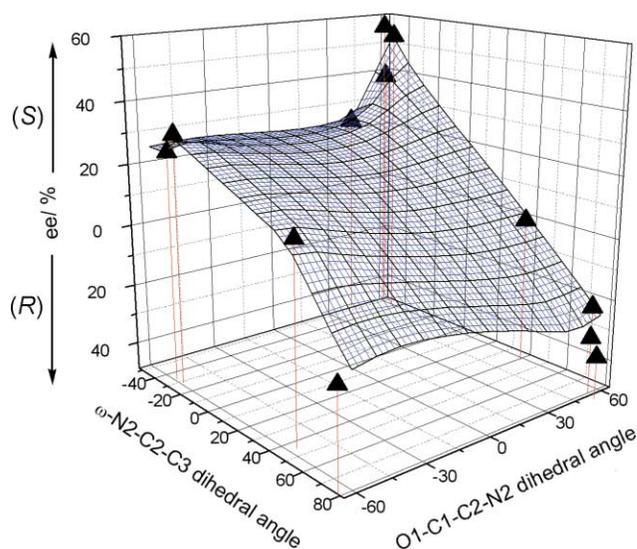
Fig. 4 Enantioselectivity surface graph for the ω–N2–C2–C3 dihedral angle *vs.* the O1–C1–C2–N2 dihedral angle. Values used are given in the caption to Fig. 3. The enhanced selectivity and greater variability at an O1–C1–C2–N2 dihedral angle of 60° (for both (*S*) and (*R*) enantiomers) is apparent. The dependency of the sense of induction on ω–N2–C2–C3 dihedral angle is once again clear also.

order **i** > **h** > **e** were observed; **4i** again proved to be the most selective ligand and highlighted that trends observed for one substrate **8** could be extended to others **9**, **10**.

Conclusions

This work demonstrates the ease with which broad ranging SARs can be developed using carbohydrate scaffolds to allow the ready and precise alteration of ligand substituent stereo-

chemistry and functionality. Although high levels of induction were not observed in the current systems, the extent of variation in enantioselectivity shows the potential for tuning over wide ranges through simple switches in ligands. For example, given the limited availability of L-glucosamines, the ability demonstrated in this system for tuning not only the level of induction but also, thus far in a limited way, the absolute sense of induction (*e.g.* **4e**⟶**4d**, 56%*S*⟶30%*R*) offers the exciting prospect of a single broadly-tuneable scaffold. At present the levels of enantioselectivity that we have generated in the current dialkylzinc–aldehyde addition system are too low to be synthetically useful but the ready chemistry that we have developed for the systematic variation of such carbohydrate ligands we believe creates a flexible method for exploring "ligand space", here allowing the rapid creation of 24 new ligands. We are currently investigating the application of this methodology in other parallel ligand families and analysing these new results in conjunction with the results presented here using more extensive factorial design techniques based on the preliminary approach that we have outlined here to create a yet more comprehensive model. Following this validation in a well-known ligand system, we intend to extend its application to other less well-explored reactions.

Experimental

Computational methods

Molecular modelling calculations were executed with MacroModel 5.5[22] on a Silicon Graphics Impact 10000 workstation using the AMBER forcefield. Monte Carlo Conformational searches were performed with default parameters and convergence criteria, sampling all conformations within 50 kJ mol^{-1} over 1000 steps. For ligands **4**, **5**, and **6f** the calculation was repeated three times, giving essentially the same results; for ligand **4g** the calculation was run over 5000 steps. All calculated global minima were then minimised again to ensure convergence. The chosen minima for **4**, **5** and **6g** were conformations in which the nitrogen lone-pair was directed away from C-1, towards C-3 and thus available to bind Zn. In all cases, the minimised conformation used was either the global minimum or less than 4 kJ mol^{-1} higher in energy than the global minimum.

Graphical analysis and methods

Surface graphs were produced using Origin 7.0 from matrices, using the correlation gridding method.

General synthetic 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 pre-coated, 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 and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1000 FT-IR spectrometer. NMR spectra were recorded on a Bruker 400 MHz or 200 MHz spectrometer, assignments of peaks were made by means of COSY, HMQC, and APT experiments. Multiplicity assignments are denoted with s, singlet; d, doublet; t, triplet *etc.* and p, pseudo. Gas chromatograms were measured using a β-CD chir-DEX, 25 m column.

Methyl *N*-acetyl-D-glucosamine 1

N-acetyl-D-glucosamine (36 g, 162.7 mmol) was dissolved in dried methanol (700 mL) and acetyl chloride (57.5 g, 732.3 mmol) was added slowly. The resulting mixture was stirred for

23 h and the solvent was evaporated to give methyl *N*-acetyl-D-glucosamine (38.2 g, 100%) as a 3 : 2 α–β anomeric mixture; mp 181 °C (MeOH–AcEt) {lit.[23] mp 166 °C, lit.[24] mp$_{βanom.}$ 195 °C (EtOH), lit.[25] mp$_{βanom.}$ 200 °C (EtOH)};[α]$_D^{24}$ + 83 (*c* 1.0, H$_2$O); {lit.[26] [α]$_{Dβanom.}^{25}$ −46.9 (*c* 2.0, H$_2$O), lit.[27] [α]$_{Dαanom.}^{25}$ +127 (*c* 1.0, H$_2$O)}; ν_{max}/cm^{-1} (KBr) 3382 (OH), 2934 (NH), 1651 (amide I), 1573 (amide II); δ_H(400 MHz, CD$_3$OD,) 4.73 (0.6H, d, *J* 3.5), 4.38 (0.4H, d, *J* 8.3), 3.96 (0.6H, dd, *J* 12.0, 1.8), 3.90 (0.4H, dd, *J* 12.0 and 1.8), 3.84 (0.4H, dd, *J* 11.9 and 2.2), 3.76–3.69 (2 H, m), 3.59–3.45 (1.4H, m), 3.40 (1.2H, s, C*H*$_3$O), 3.36 (1.8H, s, C*H*$_3$O), 3.33 (1H, m), 2.23 (1.2H, s, C*H*$_3$CO), 2.20 (1.8H, s, C*H*$_3$C(O)); δ_C(100 MHz, CD$_3$OD) 167.4 (s, CH$_3$*C*O), 107.8, 98.1 (d × 2, C-1), 77.1, 74.6, 71.5, 71.0, 70.9 (d × 5, C-2, C-3, C-4, C-5) 61.6, 61.5 (t × 2, C-6), 55.6, 48.9 (q × 2, OMe), 20.5, 20.3 (q × 2, *C*H$_3$CO); *m/z* (APCI+) 236 (M + H$^+$, 100%); (APCI$^-$): 234 ([M − H$^+$]$^-$, 100%).

Methyl 2-acetamido-4,6-*O*-benzylidine-2-deoxy-D-glucopyranoside 2[28]

Methyl *N*-acetyl-D-glucosamine, **1**, (162.7 mmol) was dissolved in DMF (400 mL); benzaldehyde dimethylacetal (48.8 mL, 325.4 mmol) and *p*-toluene sulfonic acid (0.62 g, 3.25 mmol) were added and the mixture stirred at 70 °C for 2.5 h. The reaction course was followed by mass spectrometry (APCI+, MH$^+$ = 236 ⟶ MH$^+$ = 324) and the solvent was evaporated. The residue was partitioned between CHCl$_3$ (1 L) and saturated sodium hydrogen carbonate solution (500 mL). Remaining undissolved material was removed by filtration and dissolved in hot chloroform and crystallized to give **2**. The organic layer from the partition was separated, washed with brine (300 mL), dried (MgSO$_4$), filtered and evaporated to give **2** (total **2**: 36.0 g, 69%). Recrystallisation from ethyl acetate allowed the separation of anomers.

Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside α-2 (35%). White solid; R$_f$ 0.4 (CHCl$_3$–MeOH, 9 : 1); mp 298 °C (EtOAc); [a]$_D^{24}$ + 90 (*c* 0.11, MeOH); ν_{max}/cm^{-1} (KBr) 3436 (OH), 3294 (NH), 3090 (CH, aromatic) 2990, 2946, 2912, 2872, 2834, (CH, aliphatic), 1653 (amide I), 1555 (amide II); δ_H(400 MHz, CDCl$_3$) 7.52–7.35 (5H, m, C$_6$*H*$_5$), 5.93 (1H, d, *J* 8.6, NH), 5.57 (1H, s, C*H*C$_6$H$_5$), 4.73 (1H, d, *J* 3.8, H-1), 4.29 (1H, dd, *J* 3.2 and 11.3, H-6), 4.23 (1H, ddd, *J* 3.8, 8.6 and 10.2, H-2), 3.91 (1H, pt, *J* 9.5, H-3), 3.83–3.75 (2H, m, H-5, H-6′), 3.60–3.54 (1H, m, H-4), 3.49–3.42 (1H, m, OH), 3.41 (3H, s, OMe), 2.04 (3H, s, C(O)C*H*$_3$); δ_C(100 MHz, CD$_3$OD) 171.5 (CH$_3$*C*(O)), 137.0, 129.2, 128.3, 126.3 (CC Ar), 101.9 (Ph*C*H), 98.8 (C-1), 82.0 (C-4), 70.6 (C-3), 68.8 (C-6), 62.3 (C-5), 55.2 (OMe), 54.0 (C-2), 23.3 (*C*H$_3$CO); *m/z* (TOF, ES+) 324.1447 ([M + H]$^+$, C$_{16}$H$_{22}$NO$_6$ requires 324.1442).

Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside β-2 (27%). White solid; R$_f$ 0.3 (CHCl$_3$–MeOH, 9 : 1); mp 292 °C (MeOH); [a]$_D^{24}$ −57 (*c* 0.21, MeOH) {lit.[29] [a]$_D^{25}$ −59.3 (*c* 0.56, MeOH)}; δ_H(400 MHz, CDCl$_3$) 7.45 (2H, m, C$_6$*H*$_5$), 7.23 (3H, m, C$_6$*H*$_5$), 6.08 (1H, d, *J* 6.5, NH), 5.53 (1H, s, C*H*C$_6$H$_5$), 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)C*H*$_3$); δ_C(100 MHz, CD$_3$OD) 171.5 (C=O), 137.0, 129.1, 128.3, 126.3 (C–C Ar), 102.0 (Ph*C*H), 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 (*C*H$_3$C(O)).

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside 4a, 5a[30–33]

Method 1: in a Carius tube, **2** (258 mg, 0.8 mmol) was dissolved in hydrazine monohydrate (30 mL). The sealed tube was heated to 130 °C for 12 h. Then the reaction mixture was concentrated

under reduced pressure and after flash chromatography (eluent CHCl$_3$–MeOH; 9 : 1) yielded methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside as a white solid (199 mg, 88%).

Method 2: **2** (31.84 g, 99 mmol) was added to 4 M KOH in ethanol (800 mL) and heated at reflux. After 4 h TLC (9 : 1; CHCl$_3$–MeOH) showed completion of the reaction and the mixture 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 to give crude product (23.1 g). Flash chromatography (CHCl$_3$–MeOH; 9 : 1) gave **4a–5a** (19.5 g, 70%). Further flash chromatography (CHCl$_3$–MeOH; gradient: 9 : 1–5 : 1) allowed separation of **4a** and **5a**.

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside 4a. Mp 135 °C (dec), 172 °C (melt) (ethyl acetate–methanol); $[a]_D^{25}$ +103.1 (*c* 0.91, CHCl$_3$) {lit.[33] $[a]_D^{22}$ +105.2 (*c* 0.73, CHCl$_3$)}; v_{max}/cm^{-1} (KBr) 3376, 3300 (OH, NH$_2$), 3068, 3036 (CH aromatic), 2993, 2966, 2872, 2835 (CH aliphatic), 1576, 1455 (CC Aromatic); δ_H(400 MHz, CDCl$_3$)[31] 7.50–7.36 (5H, m, Ar), 5.52 (1H, s, PhC*H*), 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, OMe), 2.74 (1H, dd, *J* 9.6 and 3.5, H-2); δ_C(50 MHz, CDCl$_3$) 137.3, 129.2, 128.3, 126.4, (Ph), 101.9 (Ph*C*H), 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 (OMe); *m/z* (TOF, ES+) 282.1350 ([M + H]$^+$, C$_{14}$H$_{20}$NO$_6$ requires 282.1341).

Methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside 5a. $[a]_D^{25}$ −55.6 (*c* 0.90, CHCl$_3$) {lit.[30] $[a]_D^{22}$ −2.2 (*c* 2, CHCl$_3$)}; mp 159.5–160.5 °C (ethyl acetate–methanol); v_{max}/cm^{-1} (KBr) 3435 (NH$_2$), 3174 (OH), 2938, 2879 (CH aliphatic), 1600 (CC aromatic); δ_H(400 MHz, CDCl$_3$)[31] 7.48–7.31 (5H, m, Ph), 5.51 (1H, s, PhC*H*), 4.31 (1H, dd, *J* 10.4 and 4.9, H-6), 4.15 (1H, d, *J* 7.9, 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, OMe), 3.35–3.42 (1H, m, H-5), 2.75 (1H, dd, *J* 8.4 and 8.5, H-2); δ_C(50 MHz, CDCl$_3$) 137.2, 129.3, 128.4, 126.3, (Ph), 105.3 (C-1), 102.0 (Ph*C*H), 81.5 (C-4), 72.8 (C-3), 68.7 (C-6), 66.5 (C-5), 57.8 (C-2), 57.4 (OMe); *m/z* (TOF, ES+) 282.1351 ([M + H]$^+$, C$_{14}$H$_{20}$NO$_6$ requires 282.1341).

General procedure for alkylation of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside 4a/5a

Alkyl iodide was added to **4a** or **5a** (200 mg, 0.71 mmol) and potassium carbonate in acetonitrile (10 mL). The reaction was stirred and heated; it was monitored by TLC and NMR, further additions of alkyl halide were made as required. On completion the reaction was filtered, concentrated under reduced pressure and purified by column chromatography.

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-ethylamino-α-D-glucopyranoside 4b[34]

1.1 Equivalents of ethyl iodide (63 µL) and potassium carbonate (108 mg) were used; the reaction was heated at 60 °C for a total of 22 h, a further 0.5 equivalents of ethyl iodide (29 µL) were added after 10 h. Purification by column chromatography (5–20% MeOH–EtOAc) afforded **4b** (123 mg, 56%) as a white solid; R_f 0.1 (10% MeOH–EtOAc); mp 97–99 °C (DCM–cyclohexane) {lit.[34] mp 125–127 °C (EtOAc–petrol)}; $[a]_D^{24}$ +91 (*c* 1.30, CHCl$_3$) {lit.[34] $[a]_D^{24}$ +107 (*c* 1, CHCl$_3$)}; v_{max}/cm^{-1} (KBr) 3428br, 3296 (OH, NH), 2928, 2865 (CH, aliphatic), 1624w (NH, δ), 1454 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.51–7.49 (2H, m, Ph), 7.38–7.34 (3H, m, Ph), 5.57 (1H, s, C*H*Ph), 4.91 (1H, d, *J* 3.5, H-1), 4.26 (1H, dd, *J* 9.6 and 4.0, H-6), 4.09 (1H, pt, *J* 9.6, H-3), 3.80 (1H, ddd, *J* 10.3, 9.0 and 4.0, H-5), 3.74 (1H, pt, *J* 9.9, H-6′), 3.64 (1H, pt, *J* 9.2, H-4), 3.44 (3H, s, OCH$_3$), 3.06 (1H, dd, *J* 9.9 and 3.5, H-2), 2.98 (1H,

dq, *J* 11.7 and 7.2, NCH$_2$), 2.82 (1H, dq, *J* 11.7 and 7.2, NCH$_2$), 1.26 (3H, pt, *J* 7.1, CH$_2$C*H$_3$*); δ_C(100 MHz, CDCl$_3$) 137.0, 129.2, 128.3, 126.4 (4 × Ph), 101.9 (*C*HPh), 97.0 (C-1), 81.2 (C-4), 68.7 (C-6), 68.5 (C-3), 62.6 (C-5), 61.8 (C-2), 55.4 (OCH$_3$), 41.9 (NCH$_2$), 14.0 (CH$_2$*C*H$_3$); *m/z* (TOF, ES+) 310.1659 ([M + H]$^+$, C$_{16}$H$_{24}$NO$_5$ requires 310.1654).

Methyl 4,6-*O*-benzylidine-2-deoxy-2-*N*-ethylamino-β-D-glucopyranoside 5b

1.1 Equivalents of ethyl iodide (63 µL) and potassium carbonate (108 mg) were used; the reaction was heated at 60 °C for a total of 60 h, further portions of ethyl iodide were added after 7 h (29 µL, 0.34 mmol), 27 h (6 µL, 0.07 mmol) and 49 h (6 µL). Purification by column chromatography (2.5–10% MeOH–EtOAc) afforded **5b** (92 mg, 42%) as a white solid; R_f 0.2 (10% MeOH–EtOAc); mp 130–134 °C melts then recrystallises, melts again 147–149 °C (DCM–ether–cyclohexane); $[a]_D^{24}$ −34 (*c* 1.10, CHCl$_3$) (Found C 62.05, H 7.5, N 4.5. C$_{16}$H$_{23}$NO$_5$ requires C 62.1, H 7.5, N 4.55%); v_{max}/cm^{-1} (KBr) 3461, 3177br (NH, OH), 2957, 2877 (CH aliphatic), 1676w, 1638w (N–H δ, CC aromatic), 1478, 1451 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.52–7.49 (2H, m, Ph), 7.39–7.35 (3H, m, Ph), 5.45 (1H, s, CHPh), 4.46 (1H, d, *J* 8.1, H-1), 4.33 (1H, dd, *J* 10.4 and 4.8, H-6), 3.78 (1H, pt, *J* 10.3, H-6′), 3.75 (1H, pt, *J* 9.5, H-3), 3.55 (1H, pt, *J* 9.3, H-4), 3.55 (3H, s, OCH$_3$), 3.43 (1H, ptd, *J* 9.6 and 4.8, H-5), 2.99 (1H, dq, *J* 11.4 and 7.2, NCH$_2$), 2.76 (1H, dq, *J* 11.4 and 7.1, NCH$_2$), 2.62 (1H, dd, *J* 9.8 and 8.2, H-2), 1.14 (3H, pt, *J* 7.1, CH$_2$C*H$_3$*); δ_C(100 MHz, CDCl$_3$) 137.0, 129.2, 128.3, 126.3 (4 × Ph), 104.6 (C-1), 101.8 (*C*HPh), 81.4 (C-4), 71.2 (C-3), 68.7 (C-6), 66.2 (C-5), 63.8 (C-2), 57.1 (OCH$_3$), 42.6 (NCH$_2$), 15.2 (CH$_2$*C*H$_3$); *m/z* (TOF, ES+) 310.1654 ([M + H]$^+$, C$_{16}$H$_{24}$NO$_5$ requires 310.1654).

Methyl 4,6-*O*-benzylidine-2-deoxy-2-*N,N*-diethylamino-α-D-glucopyranoside 4c

2.1 Equivalents of ethyl iodide (120 µL) and potassium carbonate (206 mg) were used; the reaction was 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). Purification by column chromatography (0–10% MeOH–EtOAc) afforded **4c** (201 mg, 84%) as a colourless syrup; R_f 0.4 (10% MeOH–EtOAc); $[a]_D^{24}$ +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%); v_{max}/cm^{-1} (CCl$_3$) 3431br (OH), 2969, 2928, 2858 (CH, aliphatic), 1459w (CC, aromatic); δ_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$_2$C*H$_3$*); δ_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$_2$*C*H$_3$); *m/z* (TOF, ES+) 338.1974 ([M + H]$^+$, C$_{18}$H$_{28}$NO$_5$ requires 338.1967).

Methyl 4,6-*O*-benzylidine-2-deoxy-2-*N,N*-diethylamino-β-D-glucopyranoside 5c

3 Equivalents of ethyl iodide (171 mL) and 2.1 equivalents of potassium carbonate (206 mg) were used; the reaction was heated at 60 °C for a total of 49 h, further portions of ethyl iodide were added after 7 h (58 µL, 0.71 mmol) and 27 h (29 µL, 0.34 mmol). Purification by column chromatography (0–10% MeOH–EtOAc) afforded **5c** (191 mg, 80%) as a white solid; R_f 0.7 (10% MeOH–EtOAc); mp 109–112 °C (CHCl$_3$); $[a]_D^{24}$ −15 (*c* 1.24, CHCl$_3$) (Found: C 64.05, H 8.1, N 4.15. C$_{18}$H$_{27}$NO$_5$

requires C 64.05, H 8.05, N 4.15%); ν_{max}/cm^{-1} (KBr) 3374 (OH), 3040 (CH aromatic), 2971, 2932, 2874 (CH aliphatic), 1459 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.53–7.51 (2H, m, Ph), 7.38–7.31 (3H, m, Ph), 5.58 (1H, s, C*H*Ph), 4.54 (1H, d, *J* 8.5, H-1), 4.33 (1H, dd, *J* 10.4 and 5.0, H-6), 3.83 (1H, pt, *J* 10.3, H-6′), 3.69 (1H, pt, *J* 9.4, H-3), 3.63 (1H, pt, *J* 9.0, H-4), 3.52 (3H, s, OCH$_3$), 3.42 (1H, ddd, *J* 10.6, 9.1 and 5.0, H-5), 2.81 (2H, dq, *J* 13.0 and 7.3, NCH$_2$), 2.71 (2H, dq, *J* 13.0 and 6.9, NCH$_2$), 2.63 (1H, pt, *J* 9.1, H-2), 1.08 (6H, t, *J* 7.1, CH$_2$C*H$_3$*); δ_C(100 MHz, CDCl$_3$) 137.2, 129.0, 128.2, 126.3 (Ph), 103.4 (C-1), 101.5 (*C*HPh), 81.8 (C-4), 68.8 (C-6), 68.2 (C-3), 66.6 (C-5), 65.8 (C-2), 56.7 (OCH$_3$), 44.5 (*C*H$_2$CH$_3$), 14.8 (CH$_2$-*C*H$_3$); *m/z* (TOF, ES+) 338.1966 ([M + H]$^+$, C$_{18}$H$_{28}$NO$_5$ requires 338.1967).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-*n*-propylamino-α-D-glucopyranoside 4d

1.1 Equivalents of propyl iodide (76 μL) and potassium carbonate (108 mg) were used; the reaction was heated at reflux for a total of 48 h, a further portion of propyl iodide (14 μL) was added after 28 h. Purification by column chromatography (5% MeOH–CHCl$_3$) afforded **4d** as a white solid (144 mg, 63%); R_f 0.5 (5% MeOH–CHCl$_3$); mp 89.5–91 °C (DCM); $[a]_D^{24}$ +102 (*c* 1.13, CHCl$_3$); (Found: C 62.8, H 7.9, N 4.3. C$_{17}$H$_{25}$NO$_5$ requires C 63.15, H 7.8, N 4.35%); ν_{max}/cm^{-1} (KBr) 3319, 3296 (OH, NH), 3061, 3038, (CH, aromatic), 2997, 2975, 296, 2922, 2906, 2866, 2832 (CH, aliphatic), 1470, 1431 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.52–7.50 (2H, m, Ph), 7.39–7.33 (3H, m, Ph), 5.57 (1H, s, C*H*Ph), 4.84 (1H, d, *J* 3.5, H-1), 4.28 (1H, m, H-6), 3.83–3.74 (2H, m, H-5, H-6′), 3.73 (1H, pt, *J* 9.5, H-3), 3.57 (1H, pt, *J* 9.1, H-4), 3.42 (3H, s, OCH$_3$), 2.74 (1H, ddd, *J* 11.2, 8.0 and 6.4, NHC*H$_2$*), 2.63 (1H, dd, *J* 9.9 and 3.5, H-2), 2.50 (1H, ddd, *J* 11.2, 8.2 and 6.2, NHC*H$_2$*), 1.58–1.43 (2H, m, C*H$_2$*CH$_3$), 0.93 (3H, t, *J* 7.3, CH$_2$C*H$_3$*); δ_C(100 MHz, CDCl$_3$) 137.2, 129.1, 128.2, 126.4 (4 × Ph), 101.8 (*C*HPh), 98.3 (C-1), 82.0 (C-4), 69.4 (C-3), 69.1 (C-6), 63.2 (C-2), 62.3 (C-5), 55.4 (OCH$_3$), 49.5 (NH*C*H$_2$), 23.7 (*C*H$_2$CH$_3$), 11.6 (CH$_2$*C*H$_3$); *m/z* (TOF, ES+) 338.1805 ([M + H]$^+$, C$_{17}$H$_{26}$NO$_5$ requires 324.1811).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*,*N*-di-*n*-propylamino-α-D-glucopyranoside 4e

3 Equivalents of propyl iodide (208 μL) and 2.1 equivalents of potassium carbonate (206 mg) were used; the reaction was heated at reflux for a total of 48 h, a further portion of propyl iodide (138 μL) was added after 28 h. Purification by column chromatography (2% MeOH–CHCl$_3$) afforded **4e** as a colourless syrup (186 mg, 72%); R_f 0.6 (5% MeOH–CHCl$_3$); $[a]_D^{24}$ +123 (*c* 1.84, CHCl$_3$); (Found: C 65.3, H 8.6, N 3.8. C$_{20}$H$_{31}$NO$_5$ requires C 65.75, H 8.55, N 3.85%); ν_{max}/cm^{-1} (CHCl$_3$) 3438 (OH), 2936, 2933, 2874, 2842 (CH, aliphatic), 1470, 1458 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.53–7.51 (2H, m, Ph), 7.38–7.31 (3H, m, Ph), 5.59 (1H, s, C*H*Ph), 4.83 (1H, d, *J* 3.0, H-1), 4.27 (1H, dd, *J* 9.9 and 4.5, H-6), 4.09 (1H, dd, *J* 10.5 and 8.7, H-3), 3.85 (1H, ptd, *J* 9.9 and 4.5, H-5), 3.77 (1H, pt, *J* 10.1, H-6′), 3.61 (1H, pt, *J* 9.0, H-4), 3.38 (3H, s, OCH$_3$), 2.81 (1H, dd, *J* 10.5 and 3.2, H-2), 2.74 (2H, ddd, *J* 13.5, 9.0 and 7.2, NCH$_2$), 2.53 (2H, ddd, *J* 13.5, 8.7 and 4.7, NCH$_2$), 1.55–1.34 (4H, m, CH$_3$C*H$_2$*), 0.88 (6H, t, *J* 7.3, CH$_2$C*H$_3$*); δ_C(100 MHz, CDCl$_3$) 137.3, 129.0, 128.2, 126.4 (4 × Ph), 101.7, (*C*HPh), 99.1 (C-1), 83.3 (C-4), 69.2 (C-6), 65.6 (C-3), 65.0 (C-2), 62.2 (C-5), 54.8 (OCH$_3$), 52.7 (NCH$_2$), 22.3 (*C*H$_2$CH$_3$), 11.6 (CH$_2$*C*H$_3$); *m/z* (TOF, ES+) 366.2287 ([M + H]$^+$, C$_{20}$H$_{32}$NO$_5$ requires 366.2280).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-(1-piperidinyl)-α-D-glucopyranoside 4h

1.1 Equivalents of 1,5-diiodopentane (116 μL) and potassium carbonate (108 mg) were used; 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. Purification by column chromatography (2.5–15% MeOH–DCM) afforded **4h** (210 mg, 85%) as an amorphous, white solid; R_f 0.4 (10% MeOH–EtOAc); $[a]_D^{24}$ +106 (*c* 1.63, CHCl$_3$) (Found: C 65.0, H 7.7, N 4.0. C$_{19}$H$_{27}$NO$_5$ requires C 65.3, H 7.8, N 4.0%); ν_{max}/cm^{-1} (KBr) 3454br (OH), 2929, 2852 (CH, aliphatic), 1455 (CC, aromatic); δ_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$_2$C*H$_2$*, NCH$_2$CH$_2$C*H$_2$*); δ_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$_2$C*H$_2$*), 24.7 (NCH$_2$CH$_2$-*C*H$_2$); *m/z* (TOF, ES+) 350.1971 ([M + H]$^+$, C$_{19}$H$_{28}$NO$_5$ requires 350.1967).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-(1-piperidinyl)-β-D-glucopyranoside 5h

1.1 Equivalents of 1,5-diiodopentane (116 μL) and potassium carbonate 108 mg were used; 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. Purification by column chromatography (0–10% MeOH–DCM) afforded **5h** (223 mg, 90%) as an amorphous, light yellow solid; R_f 0.7 (10% MeOH–EtOAc); $[a]_D^{24}$ −22 (*c* 1.03, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3440br (OH), 2932, 2825 (CH, aliphatic), 1469, 1454 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.53–7.50 (2H, m, Ph), 7.37–7.33 (3H, m, Ph), 5.71 (1H, s, C*H*Ph), 4.53 (1H, d, *J* 8.6, H-1), 4.32 (1H, dd, *J* 10.4 and 5.1, H-6), 3.82 (1H, pt, *J* 10.4, H-6′), 3.74 (1H, pt, *J* 9.5, H-3), 3.60 (1H, pt, *J* 9.1, H-4), 3.55 (3H, s, OCH$_3$), 3.40 (1H, ddd, *J* 10.0, 9.3 and 5.0, H-5), 3.02–2.97 (2H, m, NCH$_2$), 2.55–2.51 (2H, m, NCH$_2$), 2.39 (1H, dd, *J* 9.9 and 8.6, H-2), 1.60–1.47 (6H, m, NCH$_2$C*H$_2$*, NCH$_2$CH$_2$C*H$_2$*); δ_C(100 MHz, CDCl$_3$) 137.2, 129.0, 128.2, 126.4 (4 × Ph), 102.8 (C-1), 101.5 (*C*HPh), 81.7 (C-4), 70.8 (C-2), 68.8 (C-6), 67.8 (C-3), 66.7 (C-5), 56.5 (OCH$_3$), 51.2 (br, NCH$_2$), 27.0 (NCH$_2$C*H$_2$*), 24.6 (NCH$_2$CH$_2$C*H$_2$*); *m/z* (TOF, ES+) 350.1967 ([M + H]$^+$, C$_{19}$H$_{28}$NO$_5$ requires 350.1967).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-(4-morpholinyl)-α-D-glucopyranoside 4i

1.1 Equivalents of di(2-iodoethyl)ether[35] (255 mg) and potassium carbonate (108 mg) were used; the reaction was 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. Purification by column chromatography (2.5–5% MeOH–DCM) afforded **4i** (226 mg, 0.64 mmol, 91%) as a white solid; R_f 0.4 (5% MeOH–CHCl$_3$); mp 155–157.5 °C (DCM); $[a]_D^{24}$ +92 (*c* 1.97, CHCl$_3$); (Found: C 61.5, H 7.2, N 4.0. C$_{18}$H$_{25}$NO$_6$ requires C 61.5, H 7.15, N 4.0%); ν_{max}/cm^{-1} (KBr) 3440 (OH), 3067w (CH, aromatic), 2975, 2928, 2863 (CH, aliphatic), 1458 (CC, aromatic); δ_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$_2$O), 3.66 (2H, ddd, *J* 11.1, 5.7 and 3.4, CH$_2$O), 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$_2$N), 2.70 (1H, dd, *J* 10.6 and 3.1, H-2); δ_C(100 MHz, CDCl$_3$) 137.2, 129.1, 128.2, 126.3 (4 × Ph), 101.8 (Ph*C*H), 99.3 (C-1), 83.2 (C-4), 69.1 (C-6), 68.6 (C-2), 67.8 (CH$_2$O), 65.4 (C-3), 62.2 (C-5), 54.7 (OCH$_3$), 50.3 (CH$_2$N); *m/z* (TOF, ES+) 352.1772 ([M + H]$^+$, C$_{18}$H$_{26}$NO$_6$ requires 352.1760).

Methyl 4,6-*O*-benzylidine-2-deoxy-2-(4-morpholinyl)-β-D-gluco-pyranoside 5i

1.1 Equivalents of di(2-iodoethyl)ether[35] (255 mg) and potassium carbonate (108 mg) were used; the reaction was heated at 70 °C for 24 h, then at reflux for 6 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 **5i** (188 mg, 75%) as a white solid; R_f 0.6 (5% MeOH–CHCl$_3$); mp 148–150 °C (DCM); $[a]_D^{24}$ −24 (*c* 1.73, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3460 (OH), 3032w (CH, aromatic), 2994, 2968, 2907, 2874, 2814 (CH, aliphatic), 1471, 1455 (CC, aromatic); δ_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, C*H$_2$*O), 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$_2$N), 2.63 (2H, ddd, *J* 11.3, 6.1 and 3.2, CH$_2$N), 2.43 (1H, dd, *J* 10.2 and 8.5, H-2); δ_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$_2$O), 67.71 (C-3), 66.7 (C-5), 56.6 (OCH$_3$), 50.2 (br, CH$_2$N); *m/z* (TOF, ES+) 352.1760 ([M + H]$^+$, C$_{18}$H$_{26}$NO$_6$ requires 352.1760).

Methyl 4,6-*O*-benzylidine-2-deoxy-2-di-*N*,*N*-(2-hydroxy-ethyl-amino)-β-D-glucopyranoside 4j

3 Equivalents of 2-iodoethanol (179 μL) and 2.1 equivalents of potassium carbonate (206 mg) were used; the reaction was heated at reflux for 96 h. Further portions of 2-iodoethanol (119 μL) were added after 48 h, and 60 h. Purification by column chromatography (2 : 98 : 1–10 : 90 : 1, MeOH–CCl$_3$-H–NH$_3$) afforded **4j** as an amorphous, white solid (101 mg, 39%); R_f 0.2 (5% MeOH–CHCl$_3$); $[a]_D^{24}$ +101 (c 1.34, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3429br (OH), 2926, 2873 (CH, aliphatic), 1457 (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.51–7.49 (2H, m, Ph), 7.38–7.33 (3H, m, Ph), 5.53 (1H, s, CHPh), 4.80 (1H, d, *J* 3.3, H-1), 4.26 (1H, dd, *J* 9.9 and 4.5, H-6), 4.12 (1H, dd, *J* 10.4 and 8.8, H-3), 3.81 (1H, ddd, *J* 10.2, 9.1 and 4.4, H-5), 3.73 (1H, pt, *J* 10.1, H-6′), 3.58 (1H, pt, *J* 9.2, H-4), 3.57 (2H, m, HOCH$_2$), 3.50 (2H, dpt, *J* 11.4 and 4.2, HOCH$_2$), 3.38 (3H, s, OCH$_3$), 3.05 (2H, ddd, *J* 14.4, 8.8 and 3.8, NCH$_2$), 2.92 (1H, dd, *J* 10.4 and 3.3, H-2), 2.76 (2H, ddd, *J* 14.7, 3.9 and 3.3, NCH$_2$); δ_C(100 MHz, CDCl$_3$) 137.2, 129.1, 128.2, 126.4 (4 × Ph), 101.8 (CHPh), 99.5 (C-1), 82.5 (C-4), 69.1 (C-6), 66.7 (C-3), 64.6 (C-2), 62.5 (C-5), 60.1 (CH$_2$OH), 54.9 (OCH$_3$), 52.7 (CH$_2$NH); *m/z* (TOF, ES+) 370.1870 ([M + H]$^+$, C$_{18}$H$_{28}$NO$_7$ requires 370.1866).

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidene-2-deoxy-D-gluco-pyranoside 4f/5f[34]

Diisopropylethylamine (15.5 g, 120 mmol, 20.0 eq) and TMSCl (1.3 g, 12.0 mmol, 2.0 eq.) were added to a solution of **4a/5a** (1.7 g, 6.0 mmol) in dried dichloromethane (50 mL) under nitrogen. After 3 hours stirring at room temperature, tetrabutylammonium iodide (1.1 g, 3.0 mmol, 0.5 eq.) and benzyl bromide (3.1 g, 18.0 mmol, 3.0 eq.) were added. After 72 hours, the reaction mixture was shaken with HCl (aq., 1 M, 20 mL). The organic layer was separated, dried (magnesium sulfate), filtered and concentrated under reduced pressure. The residue was dissolved in a solution of tetrabutylammonium fluoride in THF (1 M, 10 mL) and stirred under nitrogen. After 16 h, the solvent was removed and the residue purified by flash chromatography (eluent EtOAc–hexane; 5 : 5) to give **4f/5f** (1.37 g, 61%); **4f** and **5f** may be separated by flash chromatography (2 : 1 cyclohexane–EtOAc) and and/or by recrystallization (cyclohexane–EtOAc).

Using an essentially identical procedure pure **4a** (1.42 g, 5.05 mmol) yielded **4f** (1.06 g, 56%). During this procedure a

small sample taken prior to aqueous workup was purified by flash chromatography (eluent hexane–EtOAc; 9 : 1) to give methyl 2-*N*-benzylamino-3-*O*-trimethylsilyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside; $[a]_D^{24}$ + 48 (*c* 0.2, CHCl$_3$); δ_H(250 MHz, CDCl$_3$) 7.33–7.50 (10H, m, Ph), 5.50 (1H, s, PhC*H*), 4.67 (1H, d, *J* 3.8, H-1), 4.25 (1H, dd, *J* 8.9, *J* 4.5), 3.99 (1H, pt, *J* 8.8), 3.74 (2H, m), 3.36 (3H, s, CH$_3$O), 3.43 (1H, pt, *J* 9.8), 2.77 (1H, dd, *J* 9.8, *J* 3.9, H-2), 1.95 (1H, br s, NH), 0.13 (9H, s, (CH$_3$)$_3$Si); δ_C(62.9 MHz, CDCl$_3$) 139.4, 137.4, (s × 2, Ph), 128.3, 128.1, 127.9, 126.9, 126.1 (t × 5, Ph), 101.6 (d, PhC*H*), 96.6 (d, C-1), 82.5, 71.9, 66.1, 62.7 (d × 4, C-2, C-3, C-4, C-5), 69.1 (t, C-6), 55.1 (q, CH$_3$O), 52.1 (t, C$_6$H$_5$CH$_2$), 0.6 (q, (CH$_3$)$_3$Si).

Using an essentially identical procedure pure **5a** (0.62 g, 2.21 mmol) yielded **5f** (0.5 g, 61% yield). During this procedure a small sample taken prior to aqueous workup was purified by flash chromatography (eluent hexane–EtOAc; 9 : 1) to give methyl 2-*N*-benzylamino-3-*O*-trimethylsilyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside; $[a]_D^{24}$ −73 (*c* 0.1, CHCl$_3$); δ_H(250 MHz, CDCl$_3$) 7.36–7.48 (10H, m, Ph), 5.49 (1H, s, PhC*H*), 4.34 (1H, d, *J* 8.3, H-1), 4.31 (1H, dd, *J* 5.1, *J* 4.5), 3.65–4.09 (3H, m), 3.32–3.57 (3H, m), 2.68 (1H, dd, *J* 9.0 and 8.4, H-2), 1.9 (1H, br s, NH), 0.60 (9H, s, (CH$_3$)$_3$Si); δ_C(62.9 MHz, CDCl$_3$) 140.6, 137.2 (s × 2, Ph), 128.4, 128.3, 128.1, 128.0, 126.9, 126.2, (t × 6, Ph), 106.4 (d, PhC*H*), 101.8 (d, C-1), 81.5, 74.0, 66.4, 64.2 (d × 4, C-2, C-3, C-4, C-5), 68.7 (t, C-6), 57.1 (q, CH$_3$O), 53.1 (t, C$_6$H$_5$CH$_2$), 0.1 (q, (CH$_3$)$_3$Si).

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside 4f. White solid (R$_f$ 0.6 (EtOAc)); mp 103 °C (hexane); ν_{max}/cm^{-1} (KBr) 3498 (OH), 3058, 3028, 3000 (CH aromatic), 2925, 2891, 2836 (CH aliphatic), 1602, 1498, 1458 (CC aromatic); $[a]_D^{25}$ +48 (*c* 0.2, CHCl$_3$) {lit.,[34] $[a]_D^{24}$ +57 (*c* 2, CHCl$_3$)}; δ_H(400 MHz, CDCl$_3$) 7.53–7.27 (10H, m, Ph), 5.55 (1H, s, PhC*H*), 4.63 (1H, d, *J* 3.5, H-1), 4.26 (1H, dd, *J* 3.6 and 8.9, H-6), 3.87 (2H, d, *J* 3.8, C$_6$H$_5$C*H$_2$*), 3.71–3.84 (3H, m, H-6′, H-3, H-4), 3.63 (1H, pt, *J* 9.5, H-5), 3.34 (3H, s, OMe), 2.70 (1H, dd, *J* 9.8 and 3.5, H-2); δ_C(50 MHz, CDCl$_3$) 140.2, 137.3 (s × 2, Ph), 129.1, 128.6, 128.2, 128.1, 127.3, 126.3, (d × 6, Ph), 101.8 (d, PhC*H*), 98.4 (d, C-1), 81.8 (d, C-5), 69.6 (C-3), 69.0 (t, C-6), 62.3, 62.5 (d × 2, C-2, C-4), 55.3 (q, OMe), 51.8 (t, C$_6$H$_5$CH$_2$); *m/z* (ES+): 765 (15%, M$_2$Na$^+$); 372 (100%, MH$^+$); 340 (35%); *m/z* (TOF, ES+) 372.1825 ([M + H]$^+$, C$_{21}$H$_{26}$NO$_5$ requires 372.1811).

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-β-D-glucopyranoside 5f. $[a]_D^{25}$ −22.4 (*c* 0.68, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3494, 3292 (OH, NH), 3086, 3062, 3036, 3020 (CH aromatic), 2966, 2899, 2870 (CH aliphatic), 1482, 1471, 1451 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.53–7.23 (10H, m, Ph), 5.54 (1H, s, PhC*H*), 4.38 (1H, d, *J* 7.9, H-1), 4.35 (1H, dd, *J* 4.9 and 10.4, H-6), 4.08 (1H, d, *J* 13.0, C$_6$H$_5$C*H$_2$*), 3.92 (1H, d, *J* 13.0, C$_6$H$_5$C*H$_2$*), 3.80 (1H, pt, *J* 10.2, H-6′), 3.69 (1H, pt, *J* 9.4, H-3), 3.57 (3H, s, OMe), 3.55 (1H, m, H-4), 3.47–3.39 (1H, m, H-5), 2.62 (1H, dd, *J* 8.0, 9.7, H-2); δ_C(50 MHz, CDCl$_3$) 140.4, 137.1, 129.2, 128.5, 128.3, 128.3, 127.0, 126.3 (Ph), 105.8 (C-1), 101.8 (PhC*H*), 81.4 (C-4), 72.0 (C-3), 68.8 (C-6), 66.3 (C-5), 63.2 (C-2), 57.2 (OMe), 52.2 (C$_6$H$_5$CH$_2$); HRMS (TOF, ES+) Calculated for C$_{21}$H$_{26}$NO$_5$ ([M + H]$^+$): 372.1811, found: 372.1815.

Methyl 2-*N*,*N*-dibenzylamino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside 4g

To a solution of **4a** (0.8 g, 2.8 mmol) and diisopropylethylamine (3.5 g, 10.0 eq., 28 mmol) in dried dichloromethane (15 mL), was added TMSCl (0.3 g, 3.1 mmol, 1.1 eq.) and the resulting mixture heated at reflux under nitrogen. After 12 hours, a small sample was removed and purified by flash chromatography (CHCl$_3$–MeOH, 20 : 1) to yield methyl 2-amino-3-*O*-trimethyl-

silyl-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside; R$_f$ 0.9 (CHCl$_3$–MeOH, 9 : 1); δ_H(250 MHz, CDCl$_3$) 7.34–7.51 (5H, m, C$_6$H$_5$), 5.51 (1H, s, PhC*H*), 4.78 (1H, d, *J* 3.3, H-1), 4.45 (1H, pt, *J* 10.2, H-6), 4.34 (1H dd, *J* 10.2 and 4.3, H-6′), 3.83 (2H, m), 3.61 (1H, t, *J* 10.2), 3.46 (1H, m), 2.13 (2H, br s, NH$_2$), 0.06 (9H, s, (CH$_3$)$_3$Si); δ_C(62.9 MHz, CDCl$_3$) 137.3 (s, Ph), 126.1, 128.1, 128.9 (t × 3, Ph), 102.7 (d, PhC*H*), 100.9 (d, C-1), 82.1, 63.0, 60.8, 57.3 (d × 4, C-2, C-3, C-4, C-5), 69.0 (t, C-6), 51.2 (q, CH$_3$O), 0.5 (q, (CH$_3$)$_3$Si). To the reaction mixture, tetra-butylammonium iodide (0.1 g, 0.3 mmol, 0.1 eq.) and benzyl bromide (1.4 g, 8.4 mmol, 3.0 eq.) were added. After 24 hours stirring at reflux under nitrogen, the reaction mixture was co-oled and a small sample removed and purified by flash chroma-tography (EtOAc–hexane, 1 : 8) to give methyl 2,2-*N*-dibenzyl-amino-3-*O*-trimethylsilyl-4,6-*O*-benzylidene-2-deoxy-D-gluco-pyranoside; R$_f$ 0.8 (EtOAc–hexane, 1 : 4); δ_H(250 MHz, CDCl$_3$) 7.30–7.45 (15H, m, Ph), 5.45 (1H, s, PhC*H*), 4.52 (1H, d, *J* 3.2, H-1), 4.45 (1H, dd, *J* 10.1 and 8.1, H-6), 3.78 (1H, m), 4.17 (1H, m), 3.64 (1H, pt, *J* 10.3), 3.42 (3H, s, CH$_3$O), 3.34 (1H, pt, *J* 9.3), 2.87 (1H, dd, *J* 9.8 and 3.3, H-2), 0.17 (9H, s, (CH$_3$)$_3$Si); δ_C(62.9 MHz, CDCl$_3$) 140.0, 136.3 (s × 2, Ph), 127.9, 127.6, 127.1, 127.0, 125.6, 125.3 (t × 6, Ph), 102.9 (d, PhC*H*), 100.9 (d, C-1), 82.5, 69.6, 61.2, 60.5 (d × 4, C-2, C-3, C-4, C-5), 68.1 (t, C-6), 54.7 (pt, C$_6$H$_5$C*H$_2$*), 55.3 (q, CH$_3$O), 0.0 (q, (CH$_3$)$_3$Si); *m*/*z* (ES+): 534 (M$^+$, 100%), 192 (20%); 128 (20%). The reaction mixture was shaken with HCl (aq., 1 M, 10 mL) for 30 minutes. The organic layer was dried (magnesium sulfate), filtered, concentrated under reduced pressure and purified by flash chromatography (eluent hexane–EtOAc: 9 : 1) to give methyl 2-*N,N*-dibenzylamino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside **4g** as a white solid (0.9 g, 68%); mp 148–149 °C (EtOAc–cyclohexane); [*a*]$_D^{25}$ +49.3 (*c* 1.1, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3474 (OH), 3083, 3061, 3023, 3000 (CH aromatic), 2934, 2902, 2870, 2837 (CH aliphatic), 1602, 1493, 1466, 1454 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.56–7.26 (15H, m, Ph), 5.53 (1H, s, PhC*H*), 4.79 (1H, d, *J* 3.3, H-1), 4.37 (1H, pt, *J* 10.2, H-3), 4.27 (1H, dd, *J* 10.1 and 4.8, H-6), 4.00 (2H, d, *J* 13.6, C$_6$H$_5$C*H$_2$*), 3.94–3.82 (1H, m, H-5), 3.86 (2H, d, *J* 13.6, C$_6$H$_5$C*H$_2$*), 3.70 (1H, pt, *J* 10.2, H-6′), 3.49–3.45 (1H, m, H-4), 3.47 (3H, s, OMe), 3.06 (1H, br s, OH), 2.90 (1H, dd, *J* 3.2 and 10.5, H-2); δ_C(125.9 MHz, CDCl$_3$) 140.2, 137.5, (s × 2, Ph), 129.3, 129.0, 128.7, 128.5, 127.4, 126.5 (t × 6, Ph), 101.9 (d, PhC*H*), 100.6 (d, C-1), 83.5 (d, C-4), 69.3 (d, (C-3)), 67.5 (t, C-6), 62.1 (q, OMe), 62.0 (d, C-5), 55.4, 55.3, (t × 2, C$_6$H$_5$C*H$_2$*); *m*/*z* (ES+) 485 (M$^+$ + Na, 22%); 462 (M$^+$, 100%), 128 (65%); (TOF, ES+) 462.2287 ([M + H]$^+$, C$_{28}$H$_{32}$NO$_5$ requires 462.2280).

Methyl 2-*N,N*-dibenzylamino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside 5g

An essentially identical procedure to that used for **4a** using instead **5a** (1.2 g) yielded methyl 2-*N,N*-dibenzylamino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside **5g** (1.49g, 75%); mp 136–137 °C (ethyl acetate–cyclohexane); mp (hexane) 72 °C; [*a*]$_D^{25}$ − 73.1 (*c* 1.0, CHCl$_3$); ν_{max}/cm^{-1} (KBr) 3468 br (OH), 3060, 3028 (CH aromatic), 2930, 2868 (CH aliphatic), 1603, 1495, 1454 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.52–7.23 (15H, m, Ph), 5.50 (1H, s, PhC*H*), 4.70 (1H, d, *J* 8.5, H-1), 4.33 (1H, dd, *J* 10.6 and 4.3, H-6), 3.97 (2H, d, *J* 12.7, C$_6$H$_5$C*H$_2$*), 3.86 (1H, dd, *J* 8.4 and 10.0, H-3), 3.79 (1H, m, H-6′), 3.77 (2H, d, *J* 12.7, C$_6$H$_5$C*H$_2$*), 3.68 (3H, s, OMe), 3.44 (2H, m, H-4, H-5), 3.25 (1H, br s, OH), 2.66 (1H, dd, *J* 8.6 and 10.0, H-2); δ_C(62.9 MHz, CDCl$_3$) 139.0, 137.2 (s × 2, Ph), 129.4, 129.0, 128.8, 128.5, 128.2, 127.5, 125.3 (t × 7, Ph), 103.6 (d, C-1); 101.4 (d, PhC*H*), 81.6, 66.4 (d, C-4, C-5), 68.6 (t, C-6), 68.2 (d, C-3), 63.3 (d, C-2), 56.8 (q, CH$_3$O), 54.5 (t, C$_6$H$_5$C*H$_2$*); *m*/*z* (ES+): 484 (M + Na$^+$, 22%); 462 (M + H$^+$, 100%), 128 (65%); (TOF, ES+) 462.2284 ([M + H]$^+$, C$_{28}$H$_{32}$NO$_5$ requires 462.2280).

Large scale syntheses of 2, 4a–5a, 4g, 5g from 1

Under nitrogen, **1** (75.0 g, 0.34 mol) was dissolved in dried methanol (800 mL) and acetyl chloride (53.0 g, 0.68 mol, 2.0 eq.) slowly added. After 24 hours stirring at room tempera-ture, the reaction mixture was concentrated under reduced pressure. The crude solid, benzaldehyde dimethylacetal (67.8 g, 0.45 mol, 2.0 eq.) and *p*-toluensulfonic acid (0.9 g) were dis-solved in dried dimethylformamide (500 mL). After stirring overnight at 70 °C, the reaction mixture was concentrated under reduced pressure, dissolved in chloroform (500 mL) and washed successively with 10% aqueous sodium hydrogencarbonate (250 mL) and brine (250 mL). The organic layer was dried with azeotropic distillation (2 × 250 mL of cyclohexane) and con-centrated under reduced pressure to give after recrystallisation (ethyl acetate) **2** (78.0 g, 71%).

2 (78.0 g, 0.24 mol) In ethanolic KOH (4 M, 1 L) was refluxed overnight and allowed to cool to room temperature. The reaction mixture was diluted with water (3 L) and the aqueous layer was extracted with chloroform (5 × 1 L). The organic layer was dried by azeotropic distillation (2 × 250 mL of cyclo-hexane) and recrystallized (MeOH–EtOAc) to give **4a–5a** (57.3 g, 85%).

To a solution of **4a–5a** (50.0 g, 0.18 mol) and (697 g, 5.4 mol, 30.0 eq.) of diisopropylethylamine in dried chloroform (500 mL), was added TMSCl (19.4 g, 0.20 mol, 1.1 eq.) and the resulting mixture stirred at reflux overnight. Tetrabutyl-ammonium iodide (19.9 g, 54 mmol, 0.3 eq.) and benzyl bromide (92.5 g, 0.54 mol, 3.0 eq.) were added. After 24 hours of stirring at reflux the mixture was cooled and stirred vigorously with hydrochloric acid (aq., 1 M, 500 mL) for 1 h. The organic layer was separated, dried by azeotropic distillation (2 × 250 mL of cyclohexane and 250 mL of EtOAc) to give crude **4g–5g**. The crude mixture was treated with a solution of tetrabutylammonium fluoride in THF (1 M, 260 mL). After stirring overnight at room temperature, the reaction mixture was concentrated under reduced pressure to give after recrystallisation (hexane–EtOAc, 90 : 10) **4g–5g** (59.2 g, 62%) which upon repeated recrystallization (EtOAc then EtOAc–cyclohexane) yielded **4g** (29.0 g, 30%) and **5g** (24.0 g, 25%).

Methyl 2-*N*-acetylamido-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose

Dimethyl sulfoxide (0.33 mL, 4.64 mmol) was added to di-chloromethane (20 mL) and cooled to −78 °C under a nitrogen flow. Trifluoroacetic anhydride (0.66 mL, 4.64 mmol) was added and the mixture stirred for 1 h. Methyl 2-acetamido-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside **α-2** (1 g, 3.10 mmol) was added dropwise as a solution in DCM. After a further 2 h, triethylamine (1.29 mL, 9.29 mmol) was added and the reaction was stirred for a further 2 h after which time the reaction was quenched with brine, the organic layer was dried (MgSO$_4$), and purified by flash chromatography (2.5% MeOH–DCM) to give methyl 2-*N*-acetylamido-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose (750 mg, 75% yield): [*a*]$_D^{25}$ +108.4 (*c* 0.55, CHCl$_3$); ν_{max}/cm^{-1} (KBr): 3430 br (OH), 3286 (NH), 3068 (CH aromatic), 2981, 2934, 2875 (CH aliphatic), 1740 (C=O), 1646 (amide I), 1549 (amide II), 1452 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.52–7.35 (5H, m, Ph), 6.29 (1H, d, *J* 7.8, NH), 5.59 (1H, s, PhC*H*), 5.23 (1H, d, *J* 4.3, H-1), 4.98 (1H, ddd, *J* 8.0, 4.2 and 1.2, H-2), 4.41 (2H, m, H-4, H-6), 4.09 (1H, td, *J* 9.8, 4.5, H-5), 3.97 (1H, t, *J* 10.2, H-6′), 3.40 (3H, s, OMe), 2.09 (3H, s, Ac); δ_C(100 MHz, CDCl$_3$) 195.0 (C-3), 170.1 (CH$_3$CO), 136.2, 129.4, 128.3, 126.4 (Ph), 102.0, 101.9 (C-1, PhC*H*), 82.5 (C-4), 69.4 (C-6), 66.0 (C-5), 58.9 (C-2), 55.6 (OMe), 23.0 (C*H$_3$*CO); *m*/*z* (TOF, ES+) 322.1294 ([M + H]$^+$, C$_{16}$H$_{20}$NO$_6$ requires 322.129).

Methyl 2-acetamido-4,6-*O*-benzylidine-2-deoxy-α-D-allo-pyranoside 3

Methyl 2-*N*-acetylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose (0.5 g, 1.09 mmol) in THF (20 mL) was added to L-selectride (1.31 mL, 1.0 M solution in THF) under a nitrogen atmosphere, at −78 °C. After 2 h TLC indicated completion and water (1 mL) was added dropwise. The solvent was removed under reduced pressure and the residue dried by azeotropic distillation from toluene. Purification by column chromatography (5% MeOH–DCM) gave **3** (300 mg, 60% yield); mp 159 °C (dec), 210 °C (melt) (MeOH–DCM); $[a]_D^{25}$ + 67.3 (*c* 0.855, CHCl₃); ν_{max}/cm⁻¹ (KBr) 3485, 3354 (OH, NH), 3067, 3038, 2996 (CH aromatic), 2959, 2938, 2907, 2858, 2838 (CH aliphatic), 1647 (amide I), 1529 (amide II), 1457, 1446 (CC aromatic); δ_H(400 MHz, CDCl₃) 7.51–7.35 (10H, m, Ph), 6.33 (1H, d, *J* 9.1, NH), 5.61 (1H, s, PhC*H*), 4.74 (1H, d, *J* 4.1, H-1), 4.37 (1H, dd, *J* 10.3 and 5.1, H-6), 4.29 (1H, dt, *J* 9.1 and 3.7, H-2), 4.16 (1H, m, H-3), 4.11 (1H, td, *J* 10.0 and 5.0, H-5), 3.79 (1H, pt, *J* 10.3, H-6′), 3.63 (1H, dd, *J* 9.8 and 2.8, H-4), 3.43 (3H, s, OMe), 2.82 (1H, d, *J* 6.1, OH), 2.03 (3H, s, Ac); δ_C(100 MHz, CDCl₃) 169.8 (CH₃*C*O), 137.0, 129.2, 128.3, 126.2 (Ph), 101.9 (Ph*C*H), 99.1 (C-1), 78.5 (C-4), 69.1 (C-6), 68.1 (C-3), 57.4 (C-6), 56.1 (OMe), 49.4 (C-2), 23.2 (*C*H₃CO); *m/z* (TOF, ES+) 324.1450 ([M + H]⁺, C₁₆H₂₂NO₆ requires 324.1447).

Methyl 2-*N*,*N*-dibenzylamino-3-methyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside 4l

Mp 51–53 °C; ¹H-NMR (400 MHz, CDCl₃) δ 7.49–7.46 (2H, m, Ph), 7.39–7.32 (11H, m, Ph), 7.31–7.26 (2H, m, Ph), 5.51 (1H, s, H-7), 4.84 (1H, d, *J* 3.3, H-1), 4.26 (1H, pt, *J* 4.9, H-6), 4.21 (2H, d, *J* 14.4, C*H₂*Ph), 3.82 (1H, dt, *J* 4.8 and 9.9, H-5), 3.71 (1H, d, *J* 10.4, H-6), 3.69 (2H, d, *J* 14.1, C*H₂*Ph), 3.43 (3H, s, OCH₃), 3.39 (1H, d, *J* 9.8, H-4), 3.03 (1H, s, OH), 2.96 (1H, d, *J* 3.0, H-2), 1.60 (3H, s, CH₃); δ_C(100 MHz, CDCl₃) 139.79, 137.51, 128.87, 128.72, 128.59, 128.10, 127.38, 126.26 (Ph), 101.16 (C-7), 99.17 (C-1), 84.87 (C-4), 72.94 (C-3), 69.25 (C-6), 64.75 (C-2), 61.57 (C-5), 57.16 (*C*H₂Ph), 55.10 (OCH₃), 19.21 (CH₃); *m/z* (ES+) 476 (M + H⁺).

Methyl 2-amino-4,6-*O*-benzylidine-2-deoxy-α-D-allopyranoside 6a [31,36]

Methyl 2-*N*-acetamido-4,6-*O*-benzylidine-2-deoxy-α-D-allo-pyranoside **3**, (350 mg, 1.09 mmol) was dissolved in a solution of KOH in ethanol (4 M, 8 mL) and heated at reflux for 10 h. TLC indicated completion and the reaction was diluted with DCM (30 mL), washed twice with water (15 mL), dried (MgSO₄), filtered and the solvent evaporated to give 230 mg of crude product which was purified by flash chromatography (10% MeOH–DCM) to give methyl 2-amino-4,6-*O*-benzyl-idine-2-deoxy-α-D-allopyranoside **6a** (150 mg, 49% yield); $[a]_D^{25}$ +107.4 (*c* 0.95, CHCl₃); ν_{max}/cm⁻¹ (KBr) 3385, 3312 (OH, NH), 3093 (CH aromatic), 3920, 2853 (CH aliphatic), 1573, 1455 (CC aromatic); δ_H(400 MHz, CDCl₃) [31] 7.52–7.35 (5H, m, Ph), 5.58 (1H, s, PhC*H*), 4.65 (1H, d, *J* 3.8, H-1), 4.36 (1H, dd, *J* 10.2, 5.1, H-6), 4.07 (1H, td, *J* 10.0, 4.9, H-5), 4.04 (1H, t, *J* 3.1, H-3), 3.75 (1H, t, *J* 10.4, H-6′), 3.52 (1H, dd, *J* 9.6, 2.8, H-4), 3.44 (3H, s, OMe), 2.94 (1H, t, *J* 3.4, H-2); δ_C(100 MHz, CDCl₃) 137.2, 129.2, 128.3, 126.3 (Ph), 102.0, 101.9 (Ph*C*H, C-1), 79.4 (C-4), 70.6 (C-3), 69.3 (C-6), 57.3 (C-5), 56.2 (OMe), 52.4 (C-2); *m/z* (TOF, ES+) 282.1349 ([M + H]⁺, C₁₄H₂₀NO₆ requires 282.134).

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose

Dimethylsulfoxide (0.22 mL, 3.1 mmol) was added to di-chloromethane (20 mL) and cooled to −78 °C under a nitrogen flow. Trifluoroacetic anhydride (0.44 mL, 3.1 mmol) was added and the mixture stirred for 1 h. Methyl 2-*N*-benzyl-

amino-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside **4f** (0.788 g, 2.07 mmol) was added dropwise as a solution in DCM. After a further 2 h, triethylamine (0.87 mL, 6.20 mmol) was added and the reaction was stirred for a further 5 h at room temperature, after which time the reaction was quenched with brine, the organic layer was dried (MgSO₄) and purified by column chromatography (4 : 3 ethyl acetate–cyclohexane) to give methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose (400 mg, 52% yield); ν_{max}/cm⁻¹ (KBr) 3411br (OH), 3064, 3033 (CH aromatic), 2936, 2868 (CH aliphatic), 1737 (C=O), 1605, 1579, 1497, 1453 (CC aromatic); δ_H(400 MHz, CDCl₃) 7.54–7.26 (10H, m, Ph), 5.56 (1H, s, PhC*H*), 5.04 (1H, dd, *J* 4.0 and 0.4, H-1), 4.38 (1H, dd, *J* 10.1 and 4.6, H-6), 4.27 (1H, dd, *J* 9.9 and 1.3, H-4), 4.04 (1H, td, *J* 9.9 and 4.5, H-5), 3.90 (1H, pt, *J* 10.2, H-6′), 4.05 (1H, d, *J* 13.0, C₆H₅C*H₂*), 3.76 (1H, d, *J* 13.0, C₆H₅C*H₂*), 3.57 (1H, dd, *J* 4.0 and 1.2, H-2), 3.39 (3H, s, OMe); δ_C(100 MHz, CDCl₃) 199.5 (C-3), 139.4, 136.4, 129.3, 128.5, 128.3, 128.3, 127.3, 126.4 (Ph), 104.1 (C-1), 101.9 (Ph*C*H), 82.9 (C-4), 69.6 (C-6), 66.2 (C-2), 55.5 (OMe), 51.6 (Ph*C*H₂); *m/z* (TOF, ES+) 370.1646 ([M + H]⁺, C₂₁H₂₄NO₅ 370.1654.

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-allo-pyranoside 6f

Methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose (0.35 g, 0.95 mmol) in THF (20 mL) was added to L-selectride (1.42 mL 1.0 M solution in THF) under a nitrogen atmosphere, at −78 °C. After 15 h TLC indicated completion and water (1 mL) was added dropwise. The solvent was removed under reduced pressure and the residue dried by azeotropic distillation from toluene. Purifi-cation by column chromatography (3 : 2 ethyl acetate–cyclo-hexane) gave methyl 2-*N*-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-allopyranoside **6f** (260 mg, 74% yield); mp 96.8–97.5 °C (diethyl ether); $[a]_D^{25}$ +31.7 (*c* 0.84, CHCl₃); ν_{max}/cm⁻¹ (KBr) 3499, br (OH), 3328 (NH), 3064, 3035 (CH aromatic), 2969, 2928, 2852 (CH aliphatic), 1604, 1496, 1465, 1453 (CC aro-matic); δ_H(400 MHz, CDCl₃) 7.53–7.23 (10H, m, Ph), 5.58 (1H, s, PhC*H*), 4.74 (1H, d, *J* 3.8, H-1), 4.39–4.35 (2H, m, H-3, H-6), 4.12 (1H, td, *J* 10.1 and 5.1, H-5), 3.90 (2H, d, *J* 13.1, PhC*H₂*), 3.75 (1H, pt, *J* 10.4, H-6′), 3.73 (2H, d, *J* 13.1, PhC*H₂*), 3.50 (1H, dd, *J* 9.6 and 2.8, H-4), 3.45 (3H, s, OMe), 2.85 (1H, pt, *J* 3.3, H-2), 2.80 (1H, d, *J* 5.8, OH); δ_C(100 MHz, CDCl₃) 139.7, 137.2, 129.2, 128.5, 128.3, 128.2, 127.2, 126.3 (Ph), 102.0 (Ph*C*H), 101.0 (C-1), 79.3 (C-4), 69.3 (C-6), 66.4 (C-3), 57.8 (C-5), 56.8 (C-2), 56.1 (OMe), 49.7 (Ph*C*H₂); *m/z* (TOF, ES+) 372.1815 ([M + H]⁺, C₂₁H₂₆NO₅ requires 372.1811).

Methyl 2,2-*N*,*N*-dibenzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyranoside-3-ulose

Dimethyl sulfoxide (0.23 mL, 3.25 mmol) was added to di-chloromethane (20 mL) and cooled to −78 °C under a nitrogen flow. Trifluoroacetic anhydride (0.50 mL, 3.25 mmol) was added and the mixture stirred for 1 h. Methyl 2-*N*-benzyl-amino-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyranoside, **4g** (1.0 g, 2.17 mmol) was added dropwise as a solution in DCM. After a further 2 h, triethylamine (0.90 mL, 6.51 mmol) was added and the reaction was stirred for a further 2 h at room temperature after which time the reaction was quenched with brine. The organic layer was dried (MgSO₄), filtered, the solvent removed and the residue was purified by column chromato-graphy (3 : 1 DCM–cyclohexane) to give methyl 2,2-*N*,*N*-di-benzylamino-4,6-*O*-benzylidine-2-deoxy-α-D-*ribo*-hexopyrano-side-3-ulose (800 mg, 80% yield); $[a]_D^{25}$ +48.7 (*c* 0.78, CHCl₃); ν_{max}/cm⁻¹ (KBr): 3429, br (OH), 3063, 3030 (CH aromatic), 2925, 2850 (CH aliphatic), 1744 (C=O), 1699, 1602, 1495, 1453 (CC aromatic); δ_H(400 MHz, CDCl₃) 7.54–7.24 (15H, m, Ph), 5.51 (1H, s, PhC*H*), 5.09 (1H, d, *J* 4.3, H-1), 4.36 (1H, dd, *J* 10.1, 4.8, H-6), 4.18–4.06 (2H, m, H-4, H-5), 4.09 (4H, s,

PhCH_2), 3.83 (1H, pt, J 10.1, H-6′), 3.67 (1H, d, J 4.2, H-2), 3.43 (3H, s, OMe); δ_C(100 MHz, CDCl) 199.8 (C-3), 142.7, 136.5, 129.3, 128.4, 128.3, 128.3, 127.0, 126.4 (Ph), 104.9 (C-1), 101.8 (PhCH), 82.7 (C-4), 69.4 (C-6), 66.9 (C-2), 64.4 (C-5), 56.4 (PhCH_2), 55.5 (OMe); m/z (TOF, ES+) 460.2124 ([M + H]$^+$, $C_{28}H_{30}NO_5$ requires 460.2124).

Methyl 2,-N,N-benzylamino-4,6-O-benzylidine-2-deoxy-α-D-allopyranoside 6g

Methyl 2,2-N,N-dibenzylamino-4,6-O-benzylidine-2-deoxy-α-D-ribo-hexopyranoside-3-ulose (0.100 g, 0.22 mmol) in THF (5 mL) was added to L-selectride (10.26 mL 1.0 M solution in THF) under a nitrogen atmosphere, at −78 °C. After 2 h TLC indicated completion and water (1 mL) was added dropwise. The solvent was removed under reduced pressure and the residue dried by azeotropic distillation from toluene. Purification of the residue by column chromatography (3 : 1 DCM–cyclohexane) gave methyl 2-N,N-benzylamino-4,6-O-benzylidine-2-deoxy-α-D-allopyranoside, 6g (60 mg, 60% yield); v_{max}/cm^{-1} (KBr) 3514 (OH), 3083, 3030 (CH aromatic), 2932, 2896, 2836, 2812, (CH aliphatic), 1602, 1493, 1453 (CC aromatic); δ_H(400 MHz, CDCl$_3$) 7.53–7.22 (15H, m, Ph), 5.55 (1H, s, PhCH), 4.82 (1H, d, J 3.2, H-1), 4.63, (1H, m, H-3), 4.36 (1H, dd, J 10.2 and 5.1, H-6), 4.22 (1H, td, J 10.1 and 5.1, H-5), 4.19 (2H, d, J 14.3, PhCH_2), 3.85 (2H, d, J 14.3, PhCH_2), 3.71 (1H, t, J 10.3, H-6′), 3.43 (3H, s, OMe), 3.41 (1H, dd, J 9.8 and 2.8, H-4), 3.05 (1H, d, J 6.6, OH), 2.89 (1H, dd, J 3.0 and 2.6, H-2); δ_C(100 MHz, CDCl$_3$) 140.4, 137.2 129.1, 128.5, 128.3, 128.3, 126.9, 126.3 (Ph), 102.4 (C-1), 101.8 (PhCH), 79.8 (C-4), 69.2 (C-6), 67.3 (C-3), 58.9, 58.4 (C-2, C-5), 55.9 (OMe), 55.4 (PhCH_2); m/z (TOF, ES+) 462.2285 ([M + H]$^+$, $C_{28}H_{32}NO_5$ requires 462.2280).

Methyl 4,6-O-benzylidine-2-deoxy-2-N-p-toluenesulfonamido-α-D-glucopyranoside 4k [33]

Methyl 2-amino-4,6-O-benzylidine-2-deoxy-α-D-glucopyranoside 4a (100 mg, 0.356 mmol) and sodium carbonate (81 mg, 0.427 mmol) were dissolved in 1 : 1 water–dioxan (3 mL) at 0 °C; p-toluenesulfonyl chloride (45 mg, 0.427 mmol) was added and the reaction was stirred for 2.5 h. Evaporation of the solvents gave a residue, to which chloroform was added, this was washed with water (10 mL) and brine (10 mL) then dried (MgSO$_4$), filtered and the solvent removed. Purification of the residue by column chromatography gave methyl 4,6-O-benzylidine-2-deoxy-N-p-toluenesulfonamido-α-D-glucopyranoside 4k (116 mg, 75%); v_{max}/cm^{-1} (KBr): 3552 (OH), 3336 (NH), 3081, 3068, 3036 (CH, aromatic), 2987, 2960, 2918, 2905, 2880, 2836 (CH, aliphatic), 1598, 1453 cm^{-1} (CC, aromatic); δ_H(400 MHz, CDCl$_3$) 7.81 (2H, m, Ar), 7.47–7.43 (2H, m, Ar), 7.37–7.31 (5H, m, Ar), 5.51 (1H, s, PhCH), 5.08 (1H, d, J 9.6, NH), 4.38 (1H, d, J 3.8, H-1), 4.24 (1H, m, H-6), 3.84 (1H, pt, J 9.5, H-3), 3.75–3.70 (2H, m, H-5, H-6′), 3.50 (1H, pt, J 9.2, H-4), 3.40 (1H, ptd, J 9.5 and 3.9, H-2), 3.29 (3H, s, OMe), 2.43 (3H, s, CH_3C$_6$H$_4$SO$_2$); δ_C(100 MHz, CDCl$_3$) 143.9, 137.6, 137.0, 129.8, 129.2, 128.3, 127.2, 126.3 (Ar), 101.9 (PhCH), 98.8 (C-1), 81.3 (C-4), 69.3 (C-3), 68.8 (C-6), 62.2 (C-5), 58.2 (C-2), 55.5 (OMe), 21.6 (CH_3C$_6$H$_4$SO$_2$); m/z (ES+) 435.97 (75, [M + H]$^+$), 452.93 (88, [M + NH$_4$]$^+$), 458 (40, [M + Na]$^+$), 888.20 (100% [2M + NH$_4$]$^+$).

Methyl 4,6-O-benzylidine-2-deoxy-2-N-p-toluenesulfonamido-α-D-allopyranoside 6k

Methyl 2-amino-4,6-O-benzylidine-2-deoxy-α-D-allopyranoside 6a (27 mg, 0.096 mmol) and sodium carbonate (22 mg, 0.115 mmol) were dissolved in 1 : 1 water–dioxan (2 mL) at 0 °C; p-toluenesulfonyl chloride (12 mg, 0.115 mmol) was added and the reaction was stirred for 3 h. Evaporation of the solvents gave a residue, to which chloroform was added, this was washed

with water (10 mL) and brine (10 mL), dried (MgSO$_4$) and the solvent removed. Purification of the residue by column chromatography gave methyl 4,6-O-benzylidine-2-N-p-toluenesulfonamido-2-deoxy-α-D-allopyranoside 6k (25 mg, 60%); $[a]_D^{25}$ +43 (c 1.01, CHCl$_3$); δ_H(400 MHz, CDCl$_3$) 7.79 (2H, m, Ar), 7.46–7.43 (2H, m, Ar), 7.38–7.34 (3H, m, Ar), 7.31 (2H, m, Ar), 5.54 (1H, s, PhCH), 5.49 (1H, d, J 10.2, NH), 4.54 (1H, d, J 4.1, H-1), 4.34 (1H, dd, J 10.4 and 5.1, H-6), 4.07 (1H, ptd, J 10.0 and 5.1, H-5), 3.91 (1H, s, br, H-3), 3.72 (1H, pt, J 10.4, H-6′), 3.60 (1H, ddd, J 10.3, 4.0 and 3.4, H-2), 3.50 (1H, dd, J 9.6 and 2.8, H-4), 3.32 (3H, s, OMe), 2.51 (1H, d, J 6.1, OH), 2.43 (3H, s, CH_3C$_6$H$_4$SO$_2$); δ_C(50 MHz, CDCl$_3$) 143.8, 138.4, 136.9, 129.9, 129.4, 128.4, 126.9, 126.3 (Ar), 102.0, 99.6 (C-1, PhCH), 69.1 (C-6), 78.3, 68.2, 57.3, 56.3, 53.3 (C-2, C-3, C-4, C-5, OMe), 21.6 (CH_3C$_6$H$_4$SO$_2$); v_{max}/cm^{-1} (KBr): 3494, 3294 (OH, NH), 3068, 3037 (CH, aromatic), 2984, 2970, 2923, 2874 (CH, aliphatic), 1599, 1498, 1454, 1433 cm^{-1} (CC, aromatic).

Methyl 4,6-O-benzylidine-α-D-arabino-hexopyranoside-2-ulose Z-oxime [14]

Hydrogen peroxide (35%, 1.38 mL, 7.12 mmol) was added dropwise to a solution of 2-amino-4,6-O-benzylidine-2-deoxy-α-D-glucopyranoside, 4a, (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 mL) were added to partially dissolve the precipitate, which formed. TLC (10% methanol–ethyl acetate) 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 over MgSO$_4$. Evaporation of the solvent under reduced pressure and purification of the residue by column chromatography (5–15% MeOH–DCM) afforded the Z-oxime (97 mg, 0.33 mmol, 46 %) as a white solid; R_f 0.7 (10% MeOH–EtOAc); mp 196–197 °C, (crystal form change at 140 °C); $[a]_D^{24}$ + 40 (c 1.16, CHCl$_3$); v_{max}/cm^{-1} (KBr) 3510, 3392 (OH), 2973, 2947, 2920, 2878 (CH aliphatic), 1642 (C=N); δ_H(400 MHz, d$_6$-DMSO) δ 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, PhCH), 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$_3$); δ_C(100 MHz, d$_6$-DMSO) 152.9 (C-2), 138.5, 129.8, 128.9, 127.2 (Ph), 101.5 (CHPh), 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]$^-$, requires 294.0978). The oxime was assigned as the Z isomer on the basis of a strong NOE enhancement between H-1 and N-OH but not between H-3 or C-3–OH and N–OH.

Methyl 2-amino-4,6-O-benzylidine-2-deoxy-α-D-manno-pyranoside, 7a

Method 1: methyl 4,6-O-benzylidine-α-D-arabino-hexopyranoside-2-ulose Z-oxime (100 mg, 0.34 mmol) solution in THF (2 mL) was added to lithium aluminium hydride (77 mg, 2.03 mmol) in THF (3 mL) at 0 °C and stirred under argon. After 5 min the temperature was allowed to increase to room temperature and after 1 h the reaction was heated to 50 °C and stirred for 4 h. TLC (15% MeOH–CHCl$_3$) indicated consumption of the starting material and formation of two more polar products; the reaction was allowed to cool then quenched with wet methanol and evaporated to dryness. Chloroform was added to the residue and the solution was filtered over Celite, concentrated and purified by column chromatography (1 : 5 : 95→1 : 10 : 90, ammonia–MeOH–CHCl$_3$) affording methyl 2-amino-4,6-O-benzylidine-2-deoxy-α-D-glucopyranoside, 4a (23 mg, 0.082 mmol, 24%) and methyl 2-amino-4,6-O-benzyl-

idine-2-deoxy-α-D-mannopyranoside, **7a** (27 mg, 0.96 mmol, 28%) as a white solid; R_f 0.1 (5% MeOH–CHCl$_3$); mp 102–105 °C; δ_H(400 MHz, CDCl$_3$) 7.52–7.49 (2H, m, Ph), 7.39–7.35 (3H, m, Ph), 5.57 (1H, s, CHPh), 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); δ_C(100 MHz, CDCl$_3$) 137.3, 129.2, 128.3, 126.3 (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]$^+$, requires 282.1341).

Method 2:[37] H$_2$SO$_4$ (conc., 91 μl) was added dropwise, with vigourous stiring, over 5 min to LiAlH$_4$ (1 M, 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, methyl 4,6-*O*-benzylidine-α-D-*arabino*-hexo-pyranoside-2-ulose *Z*-oxime (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 saturated NaHCO$_3$ solution. 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*-benzylidine-2-deoxy-α-D-glucopyranoside, **4a** (35 mg, 0.12 mmol, 36%) and methyl 2-amino-4,6-*O*-benzylidine-2-deoxy-α-D-mannopyranoside, **7a** (27 mg, 0.074 mmol, 22%) as white solids with identical spectral data to material previously prepared.

Method 3:[38] NiCl$_2$·6H$_2$O (165 mg, 1.69 mmol) was added to methyl 4,6-*O*-benzylidine-α-D-*arabino*-hexopyranoside-2-ulose *Z*-oxime (50 mg, 0.17 mmol) in methanol (4 mL) and cooled to −30 °C, NaBH$_4$ was then added portionwise over 1 h. After 4 hours at −30 °C TLC indicated no reaction, after a further 20 h at room temperature reaction was incomplete and it was heated at reflux for 5 h. The reaction was allowed to cool and brine and ethyl acetate were added, the aqueous phase was extracted with ethyl acetate (3 × 25 mL) and the combined organic extracts were washed with brine, dried (MgSO$_4$), concentrated and purified by column chromatography affording methyl 2-amino-4,6-*O*-benzylidine-2-deoxy-α-D-glucopyrano-side, **4a** (11.5 mg, 0.041 mmol, 24%) and methyl 2-amino-4,6-*O*-benzylidine-2-deoxy-α-D-mannopyranoside, **7a** (8.5 mg, 0.030 mmol, 18%) as white solids with identical spectral data to material previously prepared.

Addition of diethylzinc to aldehyde: representative procedure

All apparatus was oven dried and flushed with inert gas before use. Diethylzinc (1.82 mL, 1.1 M in toluene, 2 mmol) was added to a solution of **4a** (28.1 mg, 0.1 mmol) in toluene (2.5 mL) with stirring, under nitrogen. After 0.5 h at room temperature benzaldehyde **8** (101.6 μL, 1 mmol) was added. After 17 h the reaction was diluted with ether (15 mL) and quenched with HCl (15 mL, 1.5 M). The organic layer was separated and the aqueous layer extracted twice with ether. The combined organic layers were then concentrated and purified by column chromatography to give 1-phenyl-1-propanol **11** as a colourless oil (90 mg, 66%). The enantiomeric excess (63%) was determined by GC (β-CD chir-DEX, 25 m) and the configuration was determined by the sign of optical rotation: $[a]_D^{25}$ −30.0 (*c* 1.35, CHCl$_3$), {Lit.[39] $[a]_D$ −45.45 (*c* 5.15, CHCl$_3$) for (*S*)-1-phenyl-1-propanol}. δ_H(200 MHz, CDCl$_3$) 7.38–7.25 (5H, m, C$_6$H$_5$), 4.61 (pt, J 6.7, 1H, PhCH(OH)Et), 2.4 (1H, s, br, OH), 1.89–1.72 (2H, m, CH$_2$), 0.93 (3H, pt, J 7.4, CH$_3$).

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