Synthesis of the 2-Deoxyisomaltose Analogue of Acarbose by an Improved Route to Chiral Valieneamines

Tina M. Tagmose and Mikael Bols*

Abstract: A 2-deoxyisomaltose analogue of acarbose was stereoselectively synthesised in 11 steps with a total yield of 7% starting from 2,6-dibromo-2,6-dideoxy-D-mannono-1,4-lactone (**6**). The latter was reduced to the lactol, converted to the methyl glycoside (**7**) and hydrogenated to the methyl 6-bromo-2,6-dideoxyglycoside (**8**). Benzylation of the hydroxy groups, elimination of bromine to a 5-ene and Ferrier carbocyclisation gave (2*S*,3*R*)-2,3-bisbenzyloxycyclohex-5-enone (**12**). 1,2-addition of benzyloxymethyl lithium at −110 °C gave a 6:1 mixture of tertiary alcohols **13**; the (1*S*) isomer was the major one. Reaction with trichloroacetyl isocyanate gave a carbamate **19**, which, when dehydrated to the cyanate, spontaneously underwent [1,3] sigmatropic rearrangement to an isocyanate, which on addition of methanol gave the methylcarbamate **20**. Basic hydrolysis of this compound gave (2*R*,3*R*,5*R*)-5-amino-1-benzyloxymethyl-2,3-bis(benzyloxy)cyclohex-6-ene (**22**), which could be deprotected to 2-deoxyvalieneamine (**5**). Reaction with 2-azidoethyl 2,3,4-tri-*O*-benzyl-6-*O*-triflyl-α-D-glucopyranoside (**34**) gave the secondary amine **35**, which was completely de-*O*-protected with sodium in ammonia to give 6-deoxy-6-((1*R*,3*R*,4*R*)-3,4-dihydroxy-5-hydroxymethylcyclohex-5-enylamino)-D-glucose (**4**), the 2-deoxyisomaltose analogue of acarbose.

Keywords
cleavage reactions · enzyme inhibitors · glycosides · rearrangements · transition states

Introduction

During the last decade scientists have been keenly interested in mimicking the transition state for glycoside cleavage, particularly with the purpose of creating highly selective glycosidase inhibitors.[1] Selective glycosidase inhibitors have a number of very interesting applications such as treatment of AIDS,[2] diabetes,[3] and tumour metastasis.[4] The transition state can be divided into a glycon part and an aglycon part (Figure 1). So far most studies have limited themselves to mimicking the glycon portion, while the aglycon portion has largely been ignored.

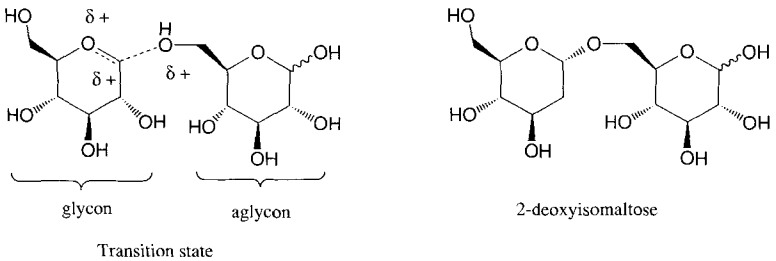

Figure 1. The transition state for glycoside cleavage, showing glycon and aglycon segments, alongside 2-deoxyisomaltose.

During recent years there has been a growing awareness that transition-state analogues that mimic both the aglycon and glycon parts will in all likelihood be more selective and potent inhibitors.[5]

We have for some years been interested in creating this type of transition-state analogue for a different purpose: the creation of catalytic antibodies that could cleave a glycosidic bond. For that purpose it was important that such analogues could mimic the entire transition state and not just a portion of it, because the antibodies were to be isolated by binding to the analogue, and if the analogue was too small, many binding antibodies could be expected to have a potential active site too small to fit the substrate. In this project we decided to try to create transition-state analogues of 2-deoxyisomaltose (6-*O*-(2-deoxy-D-*arabino*-hexopyranosyl)-D-glucose, Figure 1) with the intent of creating an antibody that could join two unequal monosaccharides in a specific manner. In order to have the best possible chance of getting a good transition-state analogue, we decided to make the four structurally diverse compounds **1**–**4** (Figure 2). The rationale behind these compounds was as follows: the piperidine **1** was the 2-deoxyisomaltose analogue of a simple piperidine used successfully to create catalytic antibodies that could cleave a tetrahydropyranyl ether.[6] Iminoglycoside **2** was based on a known potent glucosidase inhibitor modified with a L-xyloside to mimic the aglycon part. Amine **3** was made to create an antigen that would induce formation of a catalytic

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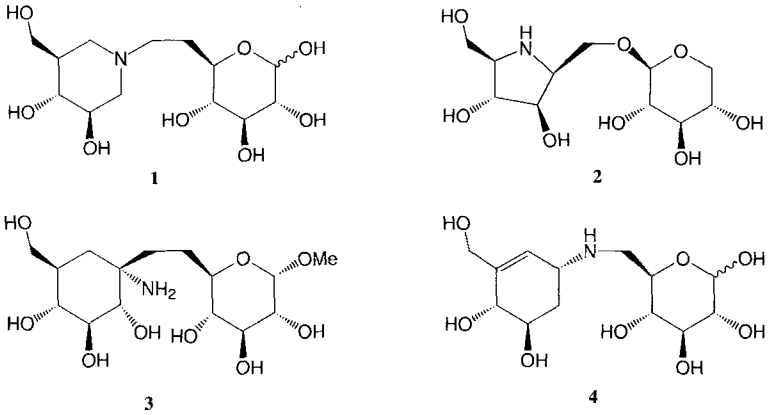

Figure 2. Four possible transition-state analogues: piperidine **1**, iminoglycoside **2**, amine **3** and the target compound, 2-deoxyisomaltose analogue **4**.

acid group in the antibody. We have previously reported the synthesis of compounds **1**–**3**.[7–10] In this paper we report the synthesis of **4**.

Acarbose[11] (Figure 3) and its analogues are the only naturally occurring glycosidase inhibitors that appear to mimic both glycon and aglycon. Indeed acarbose is extremely potent and

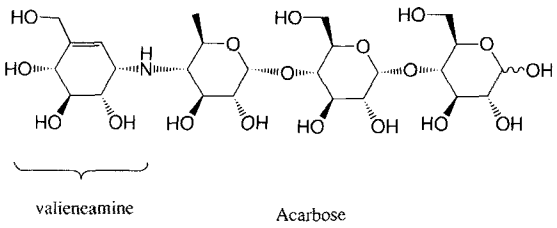

Figure 3. Acarbose, a naturally occurring glycosidase inhibitor that apparently mimics both glycon and aglycon.

selective in its inhibition. A key constituent of acarbose is the aminocyclohexene valieneamine (Figure 3). It is generally believed that valieneamine resembles the glycon of the transition state quite well, because it has a flat half-chair structure similar to an oxocarbenium ion, and the exocyclic nitrogen, when protonated, will be expected to mimic the protonated exocyclic oxygen of the glycoside substrate. A somewhat similar compound, a *manno*-valieneamine bonded to the 4-position of mannose, has been made by Brimacombe and coworkers,[12] and this compound very selectively inhibits α-mannosidase with a K_i of 30 μM. Our strategy for preparing **4** was to create a 2-deoxyisomaltose analogue of acarbose by binding the 6-position of glucose to the nitrogen of 2-deoxyvalieneamine **5**. Racemic **5** has previously been synthesised by Ogawa et al.[13] starting from functionalised cyclohexanes derived from *endo*-7-oxabicyclo[2.2.1]heptane-2 carboxylic acid in an 18-step synthesis with multiple functional conversions. No disaccharide analogue of **5** was known. Our synthetic plan therefore had to include synthesis of optically active **5**, or a precursor of **5**, and coupling that to the 6-position of a suitable glucose derivative.

Synthesis of valieneamine has been given a great deal of attention in the literature, and we therefore tried to use that information in the synthesis of our deoxy analogue. However it quickly occurred to us that most of the stereoselective syntheses[14–16] were very long, particularly because a tedious procedure of functional group conversions was carried out at the end of the synthesis to get the important trisubstituted double bond in the right position. Since in a stereoselective synthesis from a carbohydrate precursor a deoxy analogue actually is more complex to make than the fully hydroxylated compound, we needed to improve and shorten the synthesis of these molecules. We envisioned that the synthesis of valieneamine would be much shorter if substitution with the amino group could take place in an allylic fashion with the double bond rearranging into place at the same time. The synthesis of **4** was planned as shown in Figure 4. Compound **4** could be obtained from a functionalised cyclohexene with a leaving group at the allylic position, either by an S_N2' reaction or by an intramolecular substitution, to introduce a nitrogen. Either a 6-amino-6-deoxyglucose derivative could be coupled with an allylic acetate by palladium catalysis, or alternatively **5** could be coupled to a 6-triflate of glucose. Deoxyvalieneamine **5** itself could be prepared from the allylic alcohol by allylic substitution (S_N2' or palladium-catalysed) with an amine or azide. The allylic alcohol could be prepared from a cyclohexenone by 1,2-addition with benzyloxymethyllithium (Figure 4). The cyclohexenone could be made from a 2-deoxy sugar derivative by a Ferrier carbocyclisation; a 2,6-dideoxy lactone could be converted into the 2-deoxy sugar derivative, and we thus decided to start with readily available 2,6-dibromo-2,6-dideoxymannonolactone **6**.

The best synthesis of valieneamine so far actually uses a similar principle.[17] 4,5,6-tribenzyloxycyclohex-2-enone was substituted with benzyloxymethylmagnesium chloride to a tertiary alcohol that, when converted to an acetate, underwent palladium-catalysed allylic substitution with azide or benzylamine. This led to β-valieneamine. Alternatively treatment of the tertiary alcohol with thionyl chloride gave the allylically rearranged chloride, which, on nucleophilic substitution with azide, reduction and so on, led to valieneamine. The problem in this

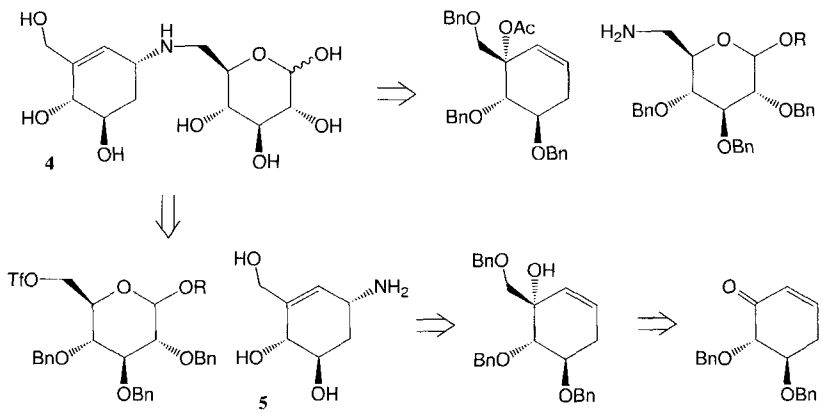

Figure 4. The planned synthesis of **4**.

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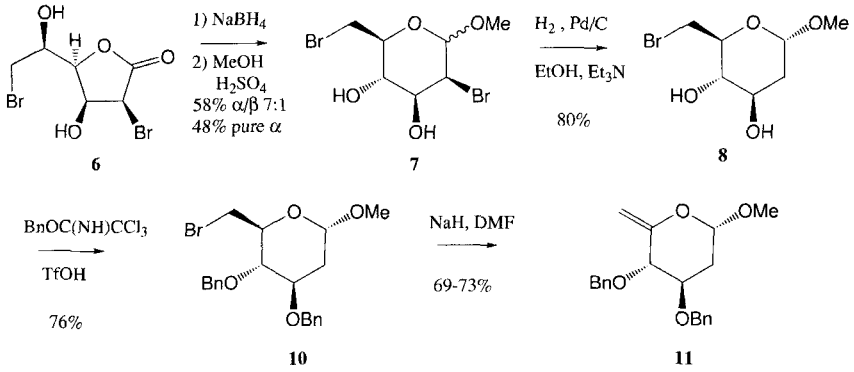
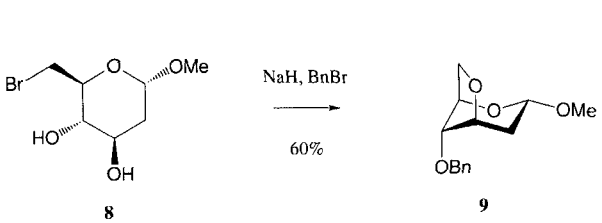
synthesis is the use of benzyloxymethylmagnesium chloride, which in our experience is unstable, unreliable and difficult to prepare.

Results and Discussion

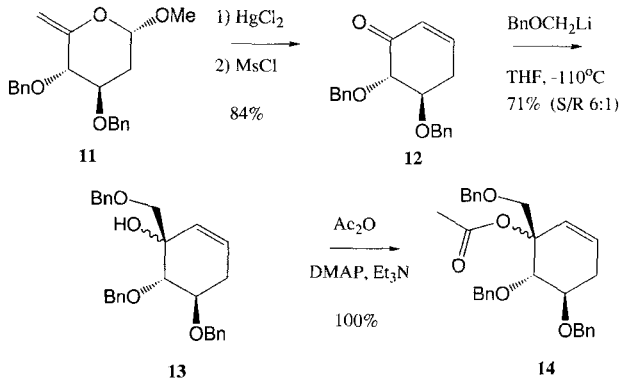
2,6-Dibromo-2,6-dideoxy-D-mannonolactone (**6**) could readily be prepared from inexpensive D-glucono-1,5-lactone in one step.[18, 19] Lactone **6** (Scheme 1) was converted to methyl-2,6-dibromo-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**7**) by reduction with sodium borohydride in the presence of acidic ion-exchange resin, to keep the pH below 6, followed by glycosidation in acidic methanol.[20] The product was a 7:1 mixture of anomers, but the α anomer, the main product, was isolated by chromatography in 48% yield. The secondary bromine was selectively reduced[20] by hydrogenation with Pd/C in the presence of triethylamine to give the 2-deoxyglycoside **8** in 80% yield. An attempt to benzylate **8** under basic conditions with sodium hydride and benzyl bromide resulted in intramolecular substitution to give methyl 3,6-anhydro-4-*O*-benzyl-2-deoxy-glucopyranoside (**9**) in good yield (Scheme 2). Instead benzylation of **8** under acidic conditions by means of Bundle's procedure was chosen,[21] which involves treatment with benzyl acetimidate and triflic acid. This gave **10** in 76% yield (Scheme 1). Elimination of the primary bromine with sodium hydride gave alkene **11** in 73% yield. Enone **12** (Scheme 3) was obtained by the Ferrier carbocyclisation[22] of **11** with mercuric chloride to give the β-hydroxycyclohexanone (some methyl 6-chloro-3,4-di-*O*-benzyl-2,6-dideoxyhexopyranoside was formed as by-product), which gave **12** after elimination with mesyl chloride in a yield of 84% (some *o*-benzyloxyphenol was formed).



Scheme 1. Conversion of lactone **6** to **7** by reduction with sodium borohydride in the presence of acidic ion-exchange resin followed by glycosidation in acidic methanol; selective reduction of **7** by hydrogenation with Pd/C in the presence of triethylamine to give the 2-deoxyglycoside **8**, and benzylation of **8** under acidic conditions by treatment with benzyl acetimidate and triflic acid to give **10**, followed by elimination with sodium hydride, to furnish alkene **11**.



Scheme 2. Intramolecular substitution of **8** under basic conditions with sodium hydride and benzyl bromide to give **9**.



Scheme 3. Ferrier carbocyclisation of **11** with mercuric chloride to give the β-hydroxycyclohexanone, which gives enone **12** after elimination with mesyl chloride. Regioselective 1,2-addition of benzyloxymethyllithium prepared in situ to **12** at −78 °C furnishes **13(1*S*)** and **13(1*R*)**. Tertiary alcohol **13** is acetylated by acetic anhydride in triethylamine catalysed by DMAP to yield **14**.

Regioselective 1,2-addition of benzyloxymethyllithium prepared in situ to the cyclohexenone **12** at −78 °C resulted in a mixture of **13(1*S*)** and **13(1*R*)** in the ratio 1:1. Lowering of the reaction temperature increased the stereoselectivity of the addition (Table 1). At −110 °C a 6:1 mixture of **13(1*S*)** to **13(1*R*)** was obtained in 71% yield. The stereochemistry of the two isomers could not be determined at this point. Attempted benzyloxymethylation of **12** with benzyloxymethyl-2-pyridylsulfone and samarium diiodide under samarium Barbier conditions[23] was, however, unsuccessful.

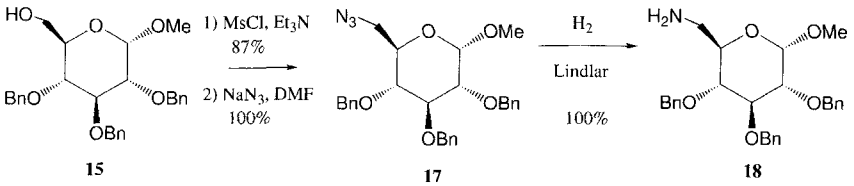
Table 1. Effect of temperature on $BnOCH_2Li$ addition to **12**.

Temperature (°C)	Yield	Ratio **13*S*:13*R***
−78	67%	1:1
−95	63%	3.4:1
−110–5	71%	6:1

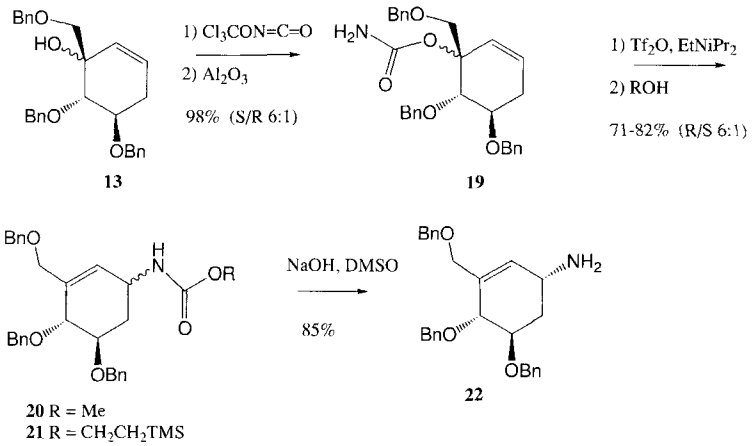
The tertiary alcohol **13** could be acetylated in very high yields by acetic anhydride in triethylamine catalysed by DMAP (Scheme 3). The isomers of **14** could be separated by flash chromatography. However, attempts to mesylate, trifluoromesylate or make a trichloroacetimidate (by reaction with base and trichloroacetonitrile) were unsuccessful owing either to decomposition or lack of reaction.

We now attempted palladium-catalysed coupling of a 6-aminoglucose derivative with allylic acetate **14**. For this purpose we synthesised a 6-aminoglucose starting from methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[24] (**15**, Scheme 4). Alcohol **15** was converted to mesylate **16**[25] in 87% yield; displacement with NaN_3 gave azide **17**[26, 27] in quantitative yield. Finally reduction with Lindlar catalyst gave amine **18**[27] in quantitative yield. All attempts to couple **18** and **14** under palladium catalysis failed, however.

Treatment of the allylic alcohol **13** with trichloroacetyl isocyanate at 0 °C in dichloromethane and subsequent filtration through aluminium oxide gave the corresponding allylcarba-



Scheme 4. Synthesis of a 6-aminoglucose starting from **15**. The alcohol **15** is converted to mesylate **16**; displacement with NaN_3 gives azide **17**, which is reduced with Lindlar catalyst to amine **18**.



Scheme 5. Treatment of allylic alcohol **13** with trichloroacetyl isocyanate at 0 °C in dichloromethane to give allylcarbamate mixture **19**; dehydration of **19** to the cyanate with triflic anhydride to give an isocyanate, which is trapped with methanol to give methylcarbamate **20**, or with 2-trimethylsilylethanol to give 2-(trimethylsilyl)ethylcarbamate (**21**); hydrolysis of **20** by aqueous sodium hydroxide in dimethylsulfoxide at 100 °C to furnish amine **22**.

mate mixture **19** in 98% yield (Scheme 5). The isomers could be separated at this point with some difficulty; however, frequently it was more convenient to carry out the subsequent reactions on the mixture. Dehydration of the allylcarbamate to the cyanate by triflic anhydride treatment resulted in a [1,3] sigmatropic rearrangement to give an isocyanate, which was trapped with methanol to give the methylcarbamate **20**. The isocyanate could alternatively be trapped with 2-trimethylsilylethanol to give 2-(trimethylsilyl)ethylcarbamate **21**. Carbamate **20** was not stable to storage at 5 °C for longer periods. On the other hand attempts to hydrolyse the isocyanate directly to the amine **22** with mineral acid or aqueous sodium hydroxide were unsuccessful because of partial formation of the urea derivative. This type of rearrangement is known to be regioselective.[28] The chirality is transferred to the newly developing asymmetric centre. When **19**(1*S*) was dehydrated, only one isomer of the methylcarbamate **20** was obtained. If a mixture of **19**(1*S*) and **19**(1*R*) was used in this reaction, the ratio of **20**(5*R*) and **20**(5*S*) was the same after the rearrangement. At this step the isomers were not separable. Hydrolysis of the methyl carbamate **20** by aqueous sodium hydroxide (10 equiv) in dimethylsulfoxide at 100 °C gave the amine **22** (Scheme 5). From a starting mixture of isomers of **20** only the major isomer of the amine **22** was isolated. When only 5 equiv of sodium hydroxide was used a mixture of isomers was obtained. This observation could be explained by an isomerisation at C-4, or more likely by decomposition of the minor isomer. A change in the solvent to ethanol or dioxane resulted in reduced yields.

Amine **22** was debenzylated by reduction with sodium in liquid ammonia, resulting in **5** with the double bond intact. Acetylation of **5** gave the corresponding tetraacetate **23**, previously prepared in racemic form by Ogawa et al.[13] Comparison of the published ^{1}H NMR chemical shifts showed that the triacetate **23** had an α-acetamido group, and hence **5** had an α-amino group as in valieneamine. With knowledge of the mechanism of the stereoselective rearrangement, the major isomer of **13** resulting from the 1,2-addition was determined to be the 1*S*-isomer **13**(1*S*), with the tertiary hydroxyl group on the same side of the ring as the neighbouring benzyloxy group. Panza et al.[17] performed a similar 1,2-addition in the synthesis of valieneamine. Use of benzyloxymethylmagnesium chloride resulted in regio- and stereoselective addition to give a cyclitol (a derivative of **13**), with the opposite relative stereochemistry at the newly formed asymmetric centre compared with **13**(1*S*). It is known that the stereoselectivity of the addition of a Grignard reagent can be the reverse of that obtained with the corresponding organolithium reagent.[29] The difference in selectivity has been explained by chelation of the magnesium to a nearby benzyl ether, which cannot occur with lithium. The same phenomenon could indeed have occurred here; this is supported by our findings that **13**(1*S*) was the major isomer.

This new synthesis of **5** consists of 11 steps from the inexpensive carbohydrate D-gluconolactone and is the first stereoselective synthesis of the compound. The synthesis could also be expected to be useful for an improved synthesis of valieneamine itself.

With **22** to hand, in order to construct **4** we needed only to carry out an electrophilic attack at nitrogen with a glucose derivative carrying a leaving group in the 6-position. Therefore a number of different glucose derivatives with leaving groups in the 6-position were prepared (Scheme 6). Since it would be desirable to be able to link the molecule to an affinity column, the azidoethyl glycosides were made. Azidoethyl glycoside **25** was prepared in 80% yield from the known[30] chloroethyl glycoside **24**. After deacetylation to the 2-azidoethyl-β-D-glucopyranoside **26**, selective tosylation of the primary alcohol to the tosylate **27** followed by persilylation gave 2,3,4-tri(trimethylsilyl) ether **28**. Tosylate **28** could be converted to iodide **29** in quantitative yield by nucleophilic substitution with potassium iodide in DMF. However, the attempted nucleophilic substitution with **22** of **27**, **28** and **29** was unsuccessful. It thus became clear that the amine **22** was a rather poor nucleophile, and that tosylate or iodide were too poor leaving groups for the reaction. Triflate therefore had to be used as leaving group. As a model experiment, alcohol **15** was converted to the 6-*O*-triflate[31] by reaction with triflic anhydride and Hünig's base and then subjected to nucleophilic substitution with cyclohexylamine. This gave methyl 2,3,4-tri-*O*-benzyl-6-(cyclohexyl)amino-6-deoxy-α-D-glucopyranoside **30** smoothly and in 78% yield.

We then prepared a suitable triflate (Scheme 6). Levoglucosane was perbenzylated to the tribenzylether **31**[32,33] and treated with 2-chloroethanol and an acid to open the 1,6-anhydride and give the 2-chloroethyl glycoside **32** in 60–76% yield.

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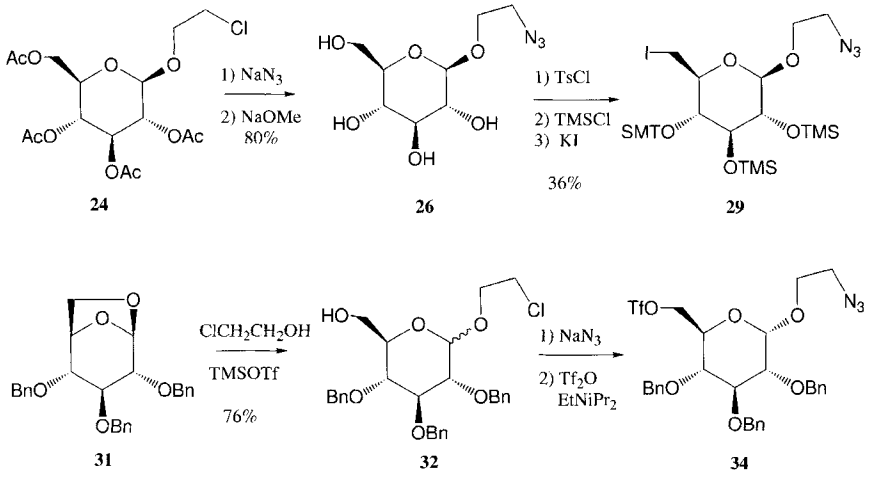
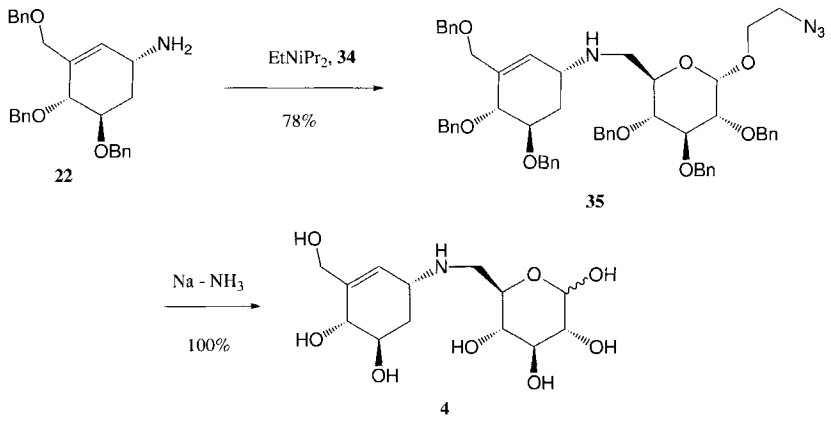


Scheme 6. Preparation of azidoethyl glycoside **25** from chloroethyl glycoside **24**, deacetylation to glucopyranoside **26**, selective tosylation to **27**, and persilylation to yield 2,3,4-tri(trimethylsilyl) ether **28**, which is converted to iodide **29** by nucleophilic substitution with potassium iodide in DMF. Treatment of the tribenzylether of levoglucosane (**31**) with 2-chloroethanol and an acid to open the 1,6-anhydride gives 2-chloroethyl glycoside **32**; nucleophilic substitution with NaN_3 (cat. KI) gives 2-azidoglycoside **33**; anomer **33α** is treated with triflic anhydride and Hünig's base to yield triflate **34**.

Nucleophilic substitution with NaN_3, with KI as catalyst, gave the 2-azidoglycoside **33** in 86% yield as a mixture of anomers. These could be separated, and for the sake of spectral simplicity the α-anomer was used henceforth. Alcohol **33α** was treated with triflic anhydride and Hünig's base to yield triflate **34**.

Amine **22** and triflate **34** were allowed to react in the presence of Hünig's base (Scheme 7). This they did smoothly to furnish the secondary amine **35** in 78% yield. Finally deprotection with sodium in liquid ammonia gave **4**.



Scheme 7. Amine **22** and triflate **34** react in the presence of Hünig's base to furnish secondary amine **35**; deprotection with sodium in liquid ammonia gives **4**.

The glycosidase inhibition of compounds **4** and **5** was investigated (Table 2). Weak inhibition of α-glucosidase by **4** at slightly acidic pH was observed, but other glycosidases were not inhibited by the compounds. Very surprisingly no inhibition of isomaltase was observed. It is possible that the lack of inhibitory activity of these compounds was caused by the lack of a 2-hydroxy group in the cyclohexene ring. In that case compound **5** might still be a good transition-state analogue for a catalytic antibody that can make 2-deoxyisomaltose. However, it might also be that the valieneamine structure is not such a good transition-state analogue. Valieneamine is a rather weak glycosidase inhibitor[34, 35] and when protonated does not have a positive charge in the ring, which might be crucial. The oligosaccharide analogues of valieneamine (acarbose, methyl acarviosine and oligostatins) are good inhibitors of α-glucosidases,[36] but it is noteworthy that inhibition by these molecules does not decrease when the double bond in the valieneamine portion of the molecules is saturated, and actually increases when water is added accross the double bond.[34, 35] This indicates that the geometry of the valieneamine structure is unimportant for the inhibition by these compounds. (Ogawa et al. have, however, recently found a decrease in inhibitory activity when the 6-hydroxy analogue of methyl acarviosine was saturated.[37, 38])

Table 2. Glycosidase inhibition (K_i in μM) of **4** and **5**.

Enzyme	**5**	**4**
α-glucosidase (bakers' yeast), pH 7.5	>800	>1000
α-glucosidase (bakers' yeast), pH 6.8	>800	321
α-glucosidase (bakers' yeast), pH 6.2	>800	450
β-glucosidase (almonds), pH 6.8	–	>1000
α-mannosidase (Jack bean), pH 5.2	–	>1000
isomaltase (yeast), pH 6.8	>1000	>1000
glycogen phosphorylase, IC_{50}	–	>356

In this paper we have presented the first stereoselective synthesis of 2-deoxyvalieneamine (**5**) and a synthesis of the corresponding isomaltose analogue **4**. It is likely that the synthetic method developed can be employed as an improved method to prepare valieneamine derivatives.

Experimental Procedure

General: ^{13}C NMR and ^1H NMR spectra were recorded on Bruker AC200, AC250 and AM500 instruments. When $CDCl_3$ was used as solvent, TMS and $CDCl_3$ (^{13}C NMR: $\delta = 76.93$) were used as references; when D_2O was used, acetone (^{13}C NMR: $\delta = 29.8$, ^1H NMR: $\delta = 2.05$) was used as reference. Mass spectra were obtained on a VG TRIO-2 instrument. Melting points were uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Microanalysis was carried out by Leo Microanalytical Laboratory, Ballerup (Denmark). Mixtures were concentrated with a rotary evaporator at a temperature below 40 °C. All reactions were performed under an atmosphere of inert gas (nitrogen or argon).

Methyl 2,6-dibromo-2,6-dideoxy-α-D-mannopyranoside (7):[19] 2,6-Dibromo-2,6-dideoxy-D-mannolactone (**6**, 10.0 g, 33 mmol) was dissolved in water (100 mL) and ethanol (50 mL) and cooled, while being stirred, to 0 °C. Ion-exchange resin (*Amberlite IR 120*, H^+, 20 mL) was added followed by sodium borohydride (1.2 g, 32 mmol) in small portions to keep the pH below 6. The reaction mixture was filtered and washed with water and methanol. Concentration of the combined filtrates gave a crude product (10.53 g). This was boiled in methanol (100 mL) containing conc. sulfuric acid (2.6 mL) for 46 h, then neutralised with pyridine and concentrated. The product was partitioned between diethylether (40 mL) and water (30 mL). The water phase was extracted twice with ether (40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give **7** as a viscous liquid in 58% yield (6.08 g, α/β 7:1). The α-isomer[20] could be isolated by

chromatography with CH_2Cl_2/MeOH 20:1 as solvent, in 48% yield (5.07 g). ^{13}C NMR ($CDCl_3$ 62.9 MHz): $\delta = 100.7$ (C-1), 71.9, 69.8, 68.9 (C-3, C-4, C-5), 55.1 (C-2), 54.4 (OCH_3), 32.9 (C-6).

Methyl 6-bromo-2,6-dideoxy-α-D-*arabino*-hexapyranoside (8): Methyl 2,6-dibromo-2,6-dideoxy-α-D-mannopyranoside (**7**, 5.24 g, 16 mmol) was dissolved in ethanol (100 mL). Triethylamine (8.1 mL) and palladium on charcoal (5%, 400 mg) were added. The solution was hydrogenated at 1 atm and 20 °C for 19 h. Filtration and concentration gave a residue from which triethylamine salts were precipitated from ethyl acetate. Concentration of the filtrate gave a viscous liquid, which was purified by flash chromatograpy in EtOAc/pentane 2:1 and 3:1 to give compound **8** in 80% yield (3.18 g). $[\alpha]_D^{22} = +109.8°$ ($c = 1.06$, $CHCl_3$); MS (CI, NH_3): $m/z = 259, 260$ (^{79}Br, ^{81}Br, $[M+NH_4^+]$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 98.4$ (C-1), 74.0, 70.4, 68.8 (C-3, C-4, C-5), 54.9 (OCH_3), 37.3, 33.7 (C-2, C-6); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 4.82$ (d, 1H, H-1, $J_{1,2} = 3.5$ Hz), 3.94 (ddd, 1H, H-3, $J_{3,4} = 11.5$, $J_{3,2ax} = 9.5$, $J_{3,2eq} = 5$ Hz), 3.74 (dd, H-6b, $J_{6a,6b} = 10.5$, $J_{6b,5} = 2$ Hz), 3.69 (ddd, 1H, H-5, $J_{5,4} = 9$, $J_{5,6a} = 5.5$ Hz), 3.63 (dd, 1H, H-6a), 3.38 (1H, H-4), 3.37 (s, 3H, OCH_3), 2.14 (ddd, 1H, H-2eq, $J_{2eq,2ax} = 13$, $J_{2eq,1} = 1$ Hz), 1.70 (ddd, 1H, H-2_{ax}); anal. calcd. for $C_7H_{13}BrO_4$: C 34.87%, H 5.34%; found: C 34.22%, H 5.70%.

Methyl 3,6-anhydro-4-*O*-benzyl-α-D-*arabino*-hexapyranoside (9): A solution of methyl 6-bromo-2,6-dideoxy-α-D-*arabino*-hexapyranoside (0.20 g, 0.8 mmol) in dry DMF (3 mL) was cooled to 0 °C, and a suspension of sodium hydride (55–65%, 0.370 g) was added. After the initial gas evolution had decreased, benzyl bromide (0.40 mL, 3.3 mmol) was added. The reaction mixture was stirred at 20 °C for 21 h, and methanol (12 mL) was added. The solvent was removed under reduced pressure. To the residue was added water (15 mL), and the aqueous phase was extracted with ether (4 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product **9** was purified by flash chromatography with hexane/ethyl acetate as eluent. A slightly yellow viscous liquid was obtained in 60% (0.120 g) yield. MS (CI, NH_3): $m/z = 268$ $[M+NH_4^+]$; ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 137$, 128.1, 127.5 (Ph), 98.0 (C-1), 75.7, 73.1, 72.3 (C-3, C-4, C-5), 71.4 (OCH_2Ph), 69.3 (C-6), 56.1 (OCH_3), 32.6 (C-2); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 7.35$ (m, 5H, Ph), 5.02 (dd, 1H, H-1, $J_{1,2ax} = 9$, $J_{1,2eq} = 4$ Hz), 4.79, 4.64 (2d, 2H, OCH_2Ph, $J = 12$ Hz), 4.44 (brs, 1H, H-5), 4.28 (t, 1H, H-3, $J_{3,4}$, $J_{3,2eq} = 4.5$ Hz), 4.17 (d, 1H, H-6b, $J_{6b,6a} = 10$ Hz), 3.93 (dd, 1H, H-6a, $J_{6a,5} = 3$ Hz), 3.78 (dd, 1H, H-4, $J_{4,5} = 2.5$ Hz), 2.11 (dd, 1H, H-2_{ax}, $J_{2ax,2eq} = 13$ Hz), 1.94 (dt, 1H, H-2_{eq}).

***Methyl* 3,4-di-*O*-benzyl-6-bromo-2,6-dideoxy-α-D-*arabino*-hexapyranoside (10)**: To a solution of methyl 6-bromo-2,6-dideoxy-α-D-*arabino*-hexapyranoside (**8**, 0.57 g, 2.4 mmol) in CH_2Cl_2 (3 mL) was added benzyltrichloroacetimidate (2.39 g, 9.5 mmol) in cyclohexane (6 mL). The solution was made weakly acidic by addition of trifluoromethanesulfonic acid (65 μL). The precipitated trichloroacetamide was filtered off and washed with CH_2Cl_2 (20 mL) after stirring at room temperature for 24 h. The organic phase was extracted with sat. $NaHCO_3$ (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$) and concentration gave a crude product, which was purified by flash chromatography with hexane/EtOAc 9:1 and 4:1, or CH_2Cl_2/pentane 10:1, to give compound **10** in 76% yield (0.76 g). $[\alpha]_D^{22} = +74.9°$ ($c = 0.95$, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 138$, 128.0, 127.6, 127.4, 127.2 (Ph), 98.1 (C-1), 79.7, 76.9 (C-3, C-4), 74.8, 71.3 (OCH_2Ph), 69.5 (C-5), 54.4 (OCH_3), 34.9, 33.8 (C-2, C-6); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.4$ (s, 10H, Ph), 4.88 (brd, 1H, H-1, $J_{1,2ax} = 3.5$ Hz), 5.03, 4.74, 4.70, 4.63 (4d, 4H, $2OCH_2Ph$, $J = 11$ Hz), 4.02 (ddd, 1H, H-3, $J_{3,2ax} = 11$, $J_{3,4} = 9$, $J_{3,2eq} = 5$ Hz), 3.82 (ddd, 1H, H-5, $J_{5,4} = 9$, $J_{5,6b} = 5$, $J_{5,6a} = 2.5$ Hz), 3.72 (dd, 1H, H-6a, $J_{6a,6b} = 10$), 3.69 (dd, 1H, H-6b), 3.53 (t, 1H, H-4), 3.37 (s, 3H, OCH_3), 2.34 (ddd, 1H, H-2_{eq}, $J_{2eq,2ax} = 13$, $J_{2eq,1} = 1$ Hz), 1.74 (ddd, 1H, H-2_{ax}); anal. calcd. for $C_{21}H_{25}BrO_4$: C 59.87%, H 5.98%, Br 18.96%; found: C 60.29%, H 5.98%, Br 19.47%.

Methyl 3,4-dibenzyloxy-α-D-*threo*-hex-5-enopyranoside (11): To a solution of methyl 3,4-di-*O*-benzyl-6-bromo-2,6-dideoxy-α-D-*arabino*-hexapyranoside (**10**, 0.209 g, 0.5 mmol) in dry DMF (3 mL) was added a suspension of sodium hydride (55–65%, 0.130 g, 3.0 mmol) at 0 °C. After this had been stirred for 24 h at 20 °C, methanol (4 mL) was added. Most of the solvent was removed by evaporation under reduced pressure, and water (20 mL) was added to the residue. The aqueous phase was extracted with ether (4 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give a viscous liquid (0.40 g). Purification by flash chromatography with hexane/EtOAc 5:1 gave the product **11** in 69% yield (0.116 g). Starting from 1.23 g **10** and prolonging the reaction time to 48 h resulted in **11** in a 73% yield. $[\alpha]_D^{22} = +27.9°$ ($c = 1.3$, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 154.7$ (C-5), 139, 128.3, 127.7, 127.5 (Ph), 99.7 (C-1), 96.8 (C-6), 79.2, 75.9 (C-3, C-4), 73.1, 72.3 (OCH_2Ph), 55.3 (OCH_3), 35.0 (C-2); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 7.35$ (m, 10H, Ph), 4.89 (t, 1H, H-1, $J_{1,2ax}$, $J_{1,2eq} = 3.5$ Hz), 4.86–4.66 (6H, 2H-6, $2OCH_2Ph$), 3.94 (m, 2H, H-3, H-4), 3.45 (s, 3H, OCH_3), 2.31 (dt, 1H, H-2_{eq}, $J_{2eq,ax} = 13$, $J_{2eq,3} = 3.5$ Hz), 1.91 (m, 1H, H-2_{ax}); anal. calcd. for $C_{21}H_{24}O_4$: C 74.09%, H 7.11%; found: C 73.75%, H 7.18%.

(2*S*,3*R*)-2,3-Bis(benzyloxy)cyclohex-5-enone (12): Methyl 3,4-dibenzyloxy-α-D-*threo*-hex-5-enopyranoside (**11**, 1.18 g, 3.5 mmol) was dissolved in acetone/water (2:1, 18 mL) by heating to reflux. Mercuric chloride (1.06 g, 3.8 mmol) was added. After reflux for 2 h, the solvent was removed on the rotary evaporator. The residue was redissolved in ether (40 mL), and aqueous potassium iodide (10%, 40 mL) was added. The aqueous phase was extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give a viscous liquid. The crude product was chromatographed with ethyl acetate/hexane 2:1 and 1:1. The purified cyclohexanone (1.03 g, 86%) and DMAP (62 mg) were dissolved in pyridine (17 mL) and cooled to 0 °C. Mesyl chloride (0.84 mL) was added dropwise. After stirring for 2.5 h at 20 °C, ice water (50 mL) was added. The aqueous phase was extracted with ether (4 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a viscous liquid (1.05 g). Purification by flash chromatography with hexane/ethyl acetate 4:1 gave the product **12** in 84% yield (0.90 g). The compound was unstable on storage. ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 197$ (C-1), 146.1 (C-5), 137.7, 128.5, 128.1, 128.0, 127.7, 127.4 (C-6, Ph), 83.9, 77.2 (C-2, C-3), 73.6, 72.5 (2 × OCH_2Ph), 32.0 (C-4); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.3$ (m, 10H, Ph), 6.81 (ddd, 1H, H-5, $J_{5,6} = 10$, $J_{5,4eq} = 5$, $J_{5,4ax} = 3$ Hz), 6.40 (ddd, 1H, H-6, $J_{6,4ax} = 3$, $J_{6,4eq} = 1$ Hz), 5.00, 4.89, 4.72, 4.64 (4d, 4H, $2OCH_2Ph$, $J = 12.0$, $J = 11.0$ Hz), 4.04 (d, 1H, H-2, $J_{2,3} = 9.5$ Hz), 3.94 (ddd, 1H, H-3, $J_{3,4ax} = 8$, $J_{3,4eq} = 5$ Hz), 2.79 (ddd, 1H, H-4_{eq}, $J_{4eq,4ax} = 18.5$ Hz), 2.50 (ddt, 1H, H-4_{ax}).

Benzyloxymethyllithium: To benzyloxymethyltributylstannane (0.140 g, 0.34 mmol) in dry THF (1.5 mL) at −78 °C under argon atmosphere was added butyllithium in hexane (1.6 M, 0.215 mL), and the solution was stirred for 10 min at −78 °C. The solution was used in situ.

(2*S*,3*R*)-2,3-Bis(benzyloxy)-1-benzyloxymethyl-1-hydroxycyclohex-5-ene (13): To a solution of benzyloxymethyllithium (0.34 mmol) in THF, prepared as described above, was added (2*S*,3*R*)-2,3-bis(benzyloxy)cyclohex-5-enone (**12**, 50 mg, 0.16 mmol) in dry THF (0.5 mL). After the reaction mixture had been stirred under an argon atmosphere at −78 °C for 2.5 h, the cooling bath was allowed to warm to 0 °C (1 h). Aqueous $NaHCO_3$ (5%, 4 mL) and ethyl acetate (6 mL) was added. The aqueous phase was extracted with ethyl acetate (4 × 6 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue (0.21 g) was purified by flash chromatography with CH_2Cl_2/acetone 150:1 to give the product **13** in 67% yield (44 mg) as a mixture of two isomers (1:1). The reaction was also carried out with the addition occurring at −90 °C or −110 °C. In those experiments the yield and the isomer ratio was 63% (1*S*:1*R* 3.4:1) or 71% (1*S*:1*R* 6:1) respectively. $[\alpha]_D^{22} = +14.4°$ ($c = 1.0$, $CHCl_3$, a 4:1 mixture); MS (CI, NH_3): $m/z = 448$ $[M+NH_4^+]$; ^{13}C NMR ($CDCl_3$, 62.9 MHz), **13(1*S*)**: $\delta = 139$, 129.1–127.4, 125.2 (Ph, C-5, C-6), 80.0, 76.1 (C-2, C-3), 75.4, 73.8, 73.3, 72.4 ($3OCH_2Ph$, C-7), 31.9 (C-4); **13(1*R*)**: $\delta = 74.3$, 73.9, 73.7, 72.0, 28.8; ^1H NMR ($CDCl_3$), **13(1*S*)**: $\delta = 7.35$ (m, 15H, Ph), 5.81 (ddd, 1H, H-5, $J_{5,6} = 10$, $J_{5,4eq} = 5.5$, $J_{5,4ax} = 2.5$ Hz), 5.61 (dd, 1H, H-6, $J_{6,4ax} = 2.5$ Hz), 4.96, 4.7–4.42 (6H, $3OCH_2Ph$), 3.96 (dt, 1H, H-3, $J_{3,4ax}$, $J_{3,2} = 9$, $J_{3,4eq} = 5.5$ Hz), 3.80 (d, 1H, H-2), 3.42 (d, 1H, H-7a, $J_{7a,7b} = 8.5$ Hz), 3.33 (d, 1H, H-7b), 2.87 (brs, 1H, OH), 2.60 (dt, 1H, H-4_{eq}, $J_{4eq,4ax} = 17.5$ Hz), 2.18 (ddt, 1H, H-4_{ax}); **13(1*R*)**: $\delta = 5.68$ (dt, 1H, H-5, $J = 10$, $J = 3.5$ Hz), 5.61 (1H, H-6), 4.7–4.42 (6H, $3OCH_2Ph$), 3.91 (d, 1H, H-2, $J = 6.5$ Hz), 3.85 (dt, 1H, H-3, $J = 6.5$, $J = 4.5$ Hz), 3.71 (d, 1H, H-7a, $J = 9.5$ Hz), 3.50 (d, 1H, H-7b), 2.47 (dm, 1H, H-4_{eq}, $J = 18$ Hz), 2.23 (dddd, 1H, H-4_{ax}, $J = 5$, $J = 3.5$, $J = 2$ Hz); anal. calcd. for $C_{28}H_{30}O_4$: C 78.11%, H 7.02%, found: C 78.04%, H 6.94%.

(2*S*,3*R*)-1-Acetoxy-2,3-bis(benzyloxy)-1-benzyloxymethylcyclohex-5-ene (14): (2*S*,3*R*)-2,3-Bis(benzyloxy)-1-benzyloxymethyl-1-hydroxycyclohex-5-ene

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(**13**, 38 mg, 0.09 mmol) and DMAP (7 mg) was dissolved in freshly distilled triethylamine (1 mL). Acetic anhydride (70 μL) was added. After this had been stirred under an argon atmosphere for 15 h at 20 °C, CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue (87 mg) was purified by flash chromatography with CH_2Cl_2/acetone 500:1, whereby the two isomers **14(1*S*)** (23 mg) and **14(1*R*)** (16 mg) were separated. Total yield: 94% (39 mg); MS (CI, NH_3): $m/z = 490$ [$M + NH_4^+$], 413 [M – AcOH +1]; ^{1}H NMR ($CDCl_3$, 250 MHz), **14(1*S*)**: $\delta = 6.21$ (ddd, 1H, H-6, $J_{5,6} = 10$, $J_{4ax,6} = 2.5$ Hz), 5.83 (ddd, 1H, H-5, $J_{4ax,5} = 3$, $J_{4eq,5} = 4.5$ Hz), 4.98, 4.76, 4.69, 4.63, 4.51, 4.42 (6d, 6H, $3OCH_2$Ph, $J \approx 12$ Hz), 4.13 (d, 1H, H-7a, $J = 8.5$ Hz), 4.08 (ddd, 1H, H-3, $J_{2,3} = 9.5$, $J_{3,4ax} = 8.5$, $J_{3,4eq} = 6$ Hz), 3.99 (d, 1H, H-2), 3.81 (d, 1H, H-7b), 2.66 (dddd, 1H, H-4_{eq}, $J_{4eq,4ax} = 18$ Hz), 2.24 (ddt, 1H, H-2_{ax}), 2.01 (s, 3H, OAc); **14(1*R*)**: $\delta = 7.3$ (Ph), 5.75 (brs, 1H), 4.82 (d, 1H, $J = 11.5$ Hz), 4.70 (d, 1H, $J = 11.5$ Hz), 4.68 (d, 1H, $J = 11.5$ Hz), 4.61 (d, 1H, $J = 11.5$ Hz), 4.58 (d, 1H, $J = 11.5$ Hz), 4.51 (d, 1H, $J = 4.5$ Hz), 4.45 (d, 1H, H-2, $J_{2,3} = 9.5$, $J = 2.3$ Hz), 3.93 (ddd, 1H, H-3, $J_{3,4ax} = 9$, $J_{3,4eq} = 6$ Hz), 3.80 (2d, 2H, H-7a, H-7b, $J = 10$ Hz), 2.54 (ddd, 1H, H-4_{eq}, $J_{4eq,4ax} = 17.5$, $J = 4$ Hz), 2.24 (dd, 1H, H-4_{ax}).

Methyl 6-amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (18):[39] To a solution of methyl 6-azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside[27] (**17**, 1.30 g, 3.1 mmol) in ethanol (80 mL) was added Lindlar catalyst (5%, 400 mg), and the mixture was hydrogenated at 1 atm and 20 °C for 3 days. Filtration and concentration gave the amine **18** in a quantitative yield (1.22 g). $[\alpha]_D^{22} = +67.0°$ ($c = 1.1$, $CHCl_3$); MS (CI, NH_3): $m/z = 464$ [M +1]; ^{13}C NMR ($CDCl_3$, 62.9 MHz, pH ≈ 7): $\delta = 138.5$, 137.9, 128.2–127.3 (Ph), 97.6 (C-1), 81.9, 79.9, 78.3 (C-2, C-3, C-4), 75.5, 74.7, 73.1 ($3OCH_2$Ph), 71.4 (C-5), 54.8 (OCH_3), 42.5 (C-6); ^{1}H NMR[27] (CD_3OD, 250 MHz): $\delta = 7.3$ (m, 15H, Ph), 4.9–4.6 (6d, 6H, $3OCH_2$Ph), 4.71 (d, 1H, H-1, $J_{1,2} = 3.5$ Hz), 3.89 (t, 1H, H-3, $J_{3,2}$, $J_{3,4} = 9.5$ Hz), 3.54 (ddd, 1H, H-5, $J_{4,5} = 9.5$, $J_{5,6b} = 7$, $J_{5,6a} = 2.5$ Hz), 3.52 (dd, 1H, H-2), 3.38 (s, 3H, OCH_3), 3.28 (t, 1H, H-4), 2.90 (dd, 1H, H-6a, $J_{6a,6b} = 13$ Hz), 2.61 (dd, 1H, H-6b).

(2*S*,3*R*)-1-Aminocarbonyloxy-2,3-bis(benzyloxy)-1-benzyloxymethylcyclohex-5-ene (19): To a solution of allyl alcohol **13** (0.405 g, 0.94 mmol) in dry dichloromethane (6 mL) was added trichloroacetyl isocyanate (167 mL, 1.4 mmol) at 0 °C. After stirring for 45 min at 0 °C and 45 min at 20 °C, the mixture was filtered through a short column of neutral Al_2O_3 and eluted with dichloromethane and dichloromethane/acetone 4:1. Concentration of the eluate gave a clear viscous liquid (0.60 g), which was purified by flash chromatography (dichloromethane/acetone 25:1 or hexane/ethyl acetate 4:1) to give the carbamate **19** as a mixture of two isomers in 98% (0.440 g) yield. On a smaller scale, the major isomer **19(1*S*)** could be separated. The compound was unstable on storage. **19(1*S*)**: $[\alpha]_D^{22} = -37.5°$ ($c = 0.87$, $CHCl_3$). **19(1*R*)**/**19(1*S*)** 9:1 mixture: $[\alpha]_D^{22} = +23.8°$ ($c = 0.84$, $CHCl_3$); MS (CI, NH_3): $m/z = 491$ [$M + NH_4^+$]; ^{13}C NMR ($CDCl_3$, 62.9 MHz), **19(1*S*)**: $\delta = 155.8$ (C=O), 138, 129.7, 128.7–127.4, 125.8 (Ph, C-5, C-6), 79.9, 75.5 (C-2, C-3), 75.8, 73.4, 72.3 ($3OCH_2$Ph), 69.4 (C-7), 32.8 (C-4); **19(1*R*)**: $\delta = 130$, 128.2–127.3, 125.8 (Ph, C-5, C-6), 85.0, 82.1, 76.7, 75.3, 73.5, 72.5; ^{1}H NMR ($CDCl_3$, 500 MHz), **19(1*S*)**: $\delta = 7.3$ (m, 15H, Ph), 6.19 (ddd, 1H, H-6, $J_{6,5} = 10$, $J_{6,4ax} = 3$, $J_{6,4eq} = 1$ Hz), 5.84 (ddd, 1H, H-5, $J_{5,4eq} = 4.5$, $J_{5,4ax} = 3$ Hz), 4.91, 4.71, 4.66, 4.59, 4.52, 4.42 (6H, $3OCH_2$Ph), 4.69 (brs, 2H, NH_2), 4.18 (d, 1H, H-7a, $J_{7a,7b} = 8.5$ Hz), 4.07 (ddd, 1H, H-3, $J_{3,2} = 10$, $J_{3,4ax} = 8.5$, $J_{3,4eq} = 6$ Hz), 3.97 (d, 1H, H-2), 3.86 (d, 1H, H-7b), 2.70 (dddd, 1H, H-4_{eq}, $J_{4eq,4ax} = 18$ Hz), 2.22 (ddt, 1H, H-4_{ax}); ^{1}H NMR ($CDCl_3$, 500 MHz), **19(1*R*)**: $\delta = 7.25$ (m, 15H, Ph), 5.83 (dd, 1H, H-6, $J_{6,5} = 10$, $J_{6,4ax} = 2.5$ Hz), 5.77 (ddd, 1H, H-5, $J_{5,4eq} = 5.5$, $J_{5,4ax} = 2$ Hz), 4.86, 4.72, 4.71, 4.61, 4.56, 4.53 (6H, $3OCH_2$Ph), 4.52 (d, 1H, H-2, $J_{2,3} = 9.5$), 4.41 (brs, 2H, NH_2), 3.97 (dt, 1H, H-3, $J_{3,4ax} = 9.5$, $J_{3,4eq} = 6$ Hz), 3.82 (s, 2H, 2H-7), 2.55 (dt, 1H, H-4_{eq}, $J_{4eq,4ax} = 17.5$ Hz), 2.28 (ddt, 1H, H-4_{ax}).

(2*R*,3*R*)-2,3-bis(benzyloxy)-1-benzyloxymethyl-5-(methoxycarbonyl)aminocyclohex-6-ene (20): To a solution of allylic carbamate **19** (151 mg, 0.32 mmol) and diisopropylethylamine (0.33 mL, 1.9 mmol) in dry dichloromethane (2 mL) at −78 °C under an argon atmosphere was added trifluoromethanesulfonic anhydride (157 mL, 0.96 mmol). The cooling bath was allowed to warm slowly to 20 °C (2 h) and stirring was continued for a further 30 min. The solvent was removed by an argon flow, and dry methanol (3 mL) was added. Stirring was continued for 75 min. The solvent was evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give the methyl carbamoyl derivative **20** (as a mixture of two isomers in the same ratio as the starting material) in 75–82% yield. The compound was unstable on storage. **20(5*R*)**: $[\alpha]_D^{22} = -89.0°$ ($c = 1.3$, $CHCl_3$); MS (CI, NH_3): $m/z = 505$ [$M + NH_4^+$]; ^{13}C NMR ($CDCl_3$, 125.8 MHz), **20(5*R*)**: $\delta = 157$ (C=O), 136 (C-6), 138.2, 128.9–127.5 (Ph), 73.4, 73.8, 73.6, 71.8, 70.8, 70.7 (C-2, C-3, C-7, 3Bn), 52.0 (OCH_3), 44.6 (C-5), 29.9 (C-4); ^{1}H NMR (C_6D_6, 500 MHz), **20(5*R*)**: $\delta = 7.3$ (m, Ph), 5.69 (brs, 1H, H-6), 4.74 (brs, 1H, NH), 4.49, 4.41, 4.36, 4.27, 4.23, 4.16 (6d, 6H, $3OCH_2$Ph), 4.42 (m, 1H, H-5), 4.20 (d, H-7a, $J_{7a,7b} = 12$ Hz), 3.97 (d, 1H, H-2, $J_{2,3} = 3$ Hz), 3.79 (d, 1H, H-7b), 3.70 (m, 1H, H-3), 3.46 (s, 3H, OCH_3), 2.08 (brdd, 1H, H-4_{eq}, $J_{4eq,4ax} = 13$, $J = 5.5$ Hz), 1.66 (brdd, 1H, H-4_{ax}, $J = 8$ Hz).

(2*R*,3*R*)-2,3-Bis(benzyloxy)-1-benzyloxymethyl-5-((2-trimethylsilyl)ethoxycarbonyl)aminocyclohex-6-ene (21): To a solution of allylic carbamate **19** (112 mg, 0.24 mmol) and diisopropylethylamine (0.24 mL, 1.4 mmol) in dry dichloromethane (1.5 mL) at −78 °C under an argon atmosphere was added trifluoromethanesulfonic anhydride (116 μL, 0.71 mmol). The reaction mixture was allowed to warm up slowly to 20 °C (2.5 h). The solvent was removed by an argon flow and dry 2-(trimethylsilyl)ethanol (0.51 mL), prepared as described in the literature,[40, 41] was added. Stirring was continued for 2.5 h. The solvent was evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate 9:1 and 4:1) to give the desired product **21** in 49% yield (68 mg) and recovered starting material in 19% yield (22 mg). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.3$ (s, 5H, Ph), 5.88 (brs, 1H, H-5), 4.72–4.36 (m, 8H), 4.20 (m, 2H), 3.99–3.83 (m, 3H), 3.74 (m, 1H), 2.24 (m, 1H, H-4_{eq}), 1.96 (m, 1H, H-4_{ax}), 0.05 (s, 11H, CH_2TMS).

(2*R*,3*R*,5*R*)-5-Amino-2,3-bis(benzyloxy)-1-benzyloxymethylcyclohex-6-ene (22) from **20**: A solution of the methyl carbamoyl derivative **20** (44 mg, 0.09 mmol) in dimethylsulfoxide (2.25 mL) and aqueous sodium hydroxide (1N, 0.9 mL) was refluxed under argon atmosphere for 30 min. Water (7.5 mL) and ethyl acetate (7.5 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 7.5 mL). The combined organics were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (ethyl acetate/methanol 20:1 and 10:1) gave the amine **22** in 85% yield (33 mg). $[\alpha]_D^{22} = -30.4°$ ($c = 0.79$, $CHCl_3$); MS (CI, NH_3): $m/z = 430$ [$M + H^+$]; ^{13}C NMR ($CDCl_3$, pH 7–8): $\delta = 138$, 128.1–127.3 (Ph), 133.8 (C-6), 133.0 (C-1), 73.3, 73.1 (C-2, C-3), 73.9, 71.4, 70.9, 70.5 (C-7, $3OCH_2$Ph), 44.1 (C-5), 33.1 (C-4); ^{1}H NMR ($CDCl_3$, pH 1): $\delta = 7.2–5$ (m, 18H, Ph, NH_3), 6.01 (s, 1H, H-6), 4.53, 4.51, 4.49, 4.42, 4.38, 4.29 (6d, 6H, $3OCH_2$Ph), 4.11 (d, H-7a, $J_{7a,7b} = 12$ Hz), 4.06 (m, 1H, H-5), 3.85 (m, 3H, H-7b, H-2, H-3), 2.42 (dt, 1H, H-4_{eq}, $J_{4eq,4ax} = 13.5$, $J = 5$ Hz), 2.01 (ddd, 1H, H-4_{ax}, $J = 9.5$, $J = 8$ Hz).

From 21: A mixture of the 2-(trimethylsilyl)ethyl carbamoyl derivative **21** (67 mg, 0.11 mmol) and tetrabutylammonium fluoride (120 mg, 0.46 mmol) in THF (1 mL) was stirred for 24 h at 20 °C. Water and ethyl acetate were added, and the aqueous layer was acidified with HCl (0.5M) and extracted three times with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (ethyl acetate/methanol 10:1) gave the amine **22** in 83% yield (39 mg).

(2*R*,3*R*,5*R*)-5-Amino-2,3-dihydroxy-1-hydroxymethylcyclohex-6-ene (5): To a solution of (2*S*,3*R*,5*R*)-5-amino-2,3-bis(benzyloxy)-1-benzyloxymethylcyclohex-6-ene (**22**, 20 mg, 43 μmol) in THF (1 mL) at −78 °C under argon atmosphere was added liquid ammonia (≈ 10 mL) followed by sodium (≈ 20 mg). The reaction mixture was blue until water (2 mL) was added after 2 h. The ammonia was evaporated by an argon flow, and the residue was concentrated and redissolved in a small amount of water and chromatographed on a CG-50 (5 mL) ion-exchange resin eluted with water. The product was concentrated with dilute HCl to give compound **5** in quantitative yield (10 mg) as its hydrochloride. $[\alpha]_D^{22} = +4.3°$ ($c = 0.8$, H_2O); ^{13}C NMR (D_2O, 62.9 MHz): $\delta = 142.9$ (C-1), 120.2 (C-6), 68.6, 67.8 (C-2, C-3), 62.3 (C-7), 45.2 (C-5), 29.5 (C-4); ^{1}H NMR (D_2O, pH 1, 500 MHz): $\delta = 5.83$ (s, 1H, H-6), 4.17 (s, 2H, 2H-7), 4.03 (m, 2H, H-2, H-3), 3.99 (m, 1H, H-5), 2.18 (dt, 1H, H-4_{eq}, $J_{4eq,4ax} = 13.5$, $J = 6.5$ Hz), 1.93 (dd, 1H, H-4_{ax}, $J = 8.5$ Hz).

(2*R*,3*R*,5*R*)-5-*N*-Acetamino-2,3-bis(acetoxy)-1-acetoxymethylcyclohex-6-ene (23): To a solution of (2*S*,3*R*,5*R*)-5-amino-2,3-bis(benzyloxy)-1-benzyloxymethylcyclohex-6-ene (**22**, 20 mg, 47 mmol) in THF (0.7 mL) at −78 °C

under argon atmosphere was added liquid ammonia (≈5 mL) followed by sodium (≈20 mg). The reaction mixture turned blue and was kept at −78 °C for 1 h. Solid ammonium chloride (60 mg) was added carefully and the blue colour disappeared. The ammonia was removed by an argon flow. The solvents were concentrated, and the residue was co-concentrated with toluene. To the residue was added pyridine (1 mL) and acetic anhydride (0.2 mL). After stirring at 20 °C for 23 h the mixture was concentrated and co-concentrated with toluene. Purification by flash chromatography with hexane/ethyl acetate 2:1, 1:1 and 1:0 as eluents gave compound **23** in 50% (7 mg) yield. $[\alpha]_D^{22} = +9.6°$ ($c = 0.55$, $CHCl_3$); MS (CI, NH_3): $m/z = 328$ $[M+1]$, 268 $[M+1-AcOH]$; ^1H NMR ($CDCl_3$): $\delta = 5.96$ (d, 1H, H-6, $J_{5,6} = 3.5$ Hz), 5.51 (d, 1H, NH, $J_{NH,5} = 8.5$ Hz), 5.37 (d, 1H, H-2, $J_{2,3} = 5$ Hz), 5.13 (ddd, 1H, H-3, $J_{3,4ax} = 8$, $J_{3,4eq} = 3$ Hz), 4.75 (m, 1H, H-5), 4.63 (d, 1H, H-7_{eq}, $J_{7a,7b} = 13$ Hz), 4.44 (d, 1H, H-7b), 2.16 (ddd, 1H, H-4_{ax}, $J_{4ax,4eq} = 13.5$, $J_{4ax,5} = 5.5$ Hz), 2.07 (s, 9H, 3OAc), 2.01 (s, 3H, OAc), 1.84 (ddd, 1H, H-4_{eq}, $J_{4eq,5} = 7$ Hz).

2-Azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (25): To a solution of 2-chloroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[30] (**24**, 1.50 g, 4.3 mmol) and potassium iodide (1.43 g, 8.6 mmol) in dry DMF (6 mL) was added sodium azide (2.81 g, 43 mmol). The reaction mixture was refluxed for 1 h, and then poured into water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crystalline product. Recrystallisation from ethyl acetate gave the product **25** as white crystals in 80% (1.53 g) yield. M.p. 115–116 °C, $[\alpha]_D^{22} = -40°$ ($c = 1.62$, $CHCl_3$) (ref. [42]: m.p. 115–116 °C, $[\alpha]_D^{22} = -41°$); ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 170.4$, 170.0, 169.1 (C=O, Ac), 100.4 (C-1), 72.5, 71.6, 70.8, 68.3, 68.0 (C-2, C-3, C-4, C-5, C-1′), 61.6 (C-6), 50.2 (C-2′), 20.4, 20.3 (CH_3, Ac); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 5.21$ (t, 1H, H-3, $J_{3,2}$, $J_{3,4} = 9.5$ Hz), 5.09 (t, 1H, H-4, $J_{4,5} = 9.5$ Hz), 5.01 (dd, 1H, H-2, $J_{2,1} = 8$ Hz), 4.59 (d, 1H, H-1), 4.25 (dd, 1H, H-6a, $J_{6a,6b} = 12.5$ Hz, $J_{6a,5} = 5$ Hz), 4.16 (dd, 1H, H-6b, $J_{6b,5} = 2.5$ Hz), 4.02 (ddd, 1H, $J_{gem} = 10.5$, $J_{vic} = 5$, $J_{vic} = 3.5$, H-1′), 3.72 (ddd, 1H, H-5), 3.68 (ddd, 1H, $J_{vic} = 8$, $J_{vis} = 3.5$, H-1′), 3.48 (ddd, 1H, $J_{gem} = 13$ Hz, H-2′), 3.29 (ddd, 1H, H-2′).

2-Azidoethyl-β-D-glucopyranoside (26): To a suspension of 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**25**, 1.22 g, 3.5 mmol) in methanol (15 mL) was added sodium methoxide in methanol (2.4 M, 0.58 mL). The mixture was stirred at room temperature for 25 min, and then the solution was neutralised by stirring with Amberlite ion-exchange resin IR 120, H^+ (10 mL) for 20 min. The Amberlite was removed by filtration and rinsed with methanol. Concentration of the filtrate and co-concentration with toluene gave a viscous liquid as crude product. Purification by flash chromatography with ethyl acetate/methanol 10:1 as eluent gave the product **26** as a clear viscous liquid in ≈100% yield (0.88 g). $[\alpha]_D^{22} = -17°$ ($c = 0.9$, MeOH); MS (CI, NH_3): $m/z = 267$ $[M+NH_4^+]$;. ^{13}C NMR (D_2O, 62.9 MHz): $\delta = 102.4$ (C-1), 76.1, 75.8, 73.2, 69.6 (C-2, C-3, C-4, C-5), 72.2 (C-1′), 64.5 (C-6), 50.7 (C-2′); ^1H NMR (D_2O): $\delta = 4.28$ (d, 1H, H-1, $J_{1,2} = 8$ Hz), 3.82 (dt, 1H, $J = 11.5$, $J = 5.0$ Hz), 3.71 (dd, $J = 12.5$, $J = 1$ Hz), 3.61 (dd, 1H, $J = 11.5$, $J = 5$ Hz), 3.51 (dd, 1H, $J = 12.5$, $J = 5$ Hz), 3.35 (m, 2H), 3.3–3.17 (m, 3H, H-2, H-3, H-5), 3.08 (t, 1H, H-4, $J = 9$ Hz); anal. calcd. for $C_8H_{15}N_3O_6 \cdot 0.37H_2O$: C 37.55, H 6.05, N 16.42; found: C 37.54, H 6.14, N 16.57.

2-Azidoethyl 6-*O*-tosyl-β-D-glucopyranoside (27): To a solution of 2-azidoethyl β-D-glucopyranoside (**26**, 0.323 g, 1.3 mmol) in pyridine (5 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.279 g). After being stirred for 22 h, the mixture was poured into aqueous HCl/ice water (0.5 N, 40 mL) and extracted with dichloromethane (3 × 30 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (20 mL) and water (20 mL), dried (Na_2SO_4) and concentrated to give a viscous liquid. Purification by flash chromatography with ethyl acetate as eluent gave the product **27** as a white foam in 73% yield (0.382 g), which could be crystallised from ethyl acetate: m.p. 133–135 °C, $[\alpha]_D^{22} = -3.2°$ ($c = 1.0$, MeOH); MS (CI, NH_3): $m/z = 421$ $[M+NH_4^+]$; ^{13}C NMR (CD_3OD, 125.8 MHz): $\delta = 134$, 129.1 (Ts), 104.5 (C-1), 77.8, 75.0, 74.8, 71.1 (C-2, C-3, C-4, C-5), 70.8, 69.6 (C-6, C-1′), 52.0 (C-2′), 21.6 (Ts); ^1H NMR (CD_3OD, 500 MHz): $\delta = 7.05$, 6.65 (2d, 4H, Ar), 4.8 (brs, 3H, 3OH), 4.34 (dd, 1H, H-6a, $J = 11_{6a,6b}$, $J_{6a,5} = 2$ Hz), 4.25 (d, H-1, $J_{1,2} = 8$ Hz), 4.14 (dd, 1H, H-6b, $J_{6b,5} = 6$ Hz), 3.85 (ddd, 1H, H-1′a, $J_{gem} = 11$, $J_{vic} = 6$, J_{vic} 4 Hz), 3.69 (ddd, 1H, H-1′b, $J_{vic} = 6$, $J_{vic} = 4$ Hz), 3.44 (ddd, 1H, H-5, $J_{5,4} = 9.5$ Hz), 3.4 (m, 2H, H-2′a, H-2′b), 3.30 (t, 1H, H-3, $J_{3,4}$, $J_{3,2} = 9$ Hz), 3.20 (t, 1H, H-4), 3.13 (dd, 1H, H-2), 2.54 (s, 3H, Ts); anal. calcd. for $C_{15}H_{21}N_3O_8S$: C 44.66, H 5.25, N 10.42, S 7.95; found: C 44.60, H 5.26, N 10.51, S 7.91.

2-Azidoethyl 6-*O*-tosyl-2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranoside (28): To a solution of 2-azidoethyl 6-*O*-tosyl-β-D-glucopyranoside (**27**, 0.469 g, 1.2 mmol) in pyridine (2 mL) was added trimethylchlorosilane (0.54 mL, 4.3 mmol). The mixture was stirred at room temperature in darkness for 15 h, and then poured into ice water (15 mL). The aqueous layer was extracted with dichloromethane (4 × 40 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a clear viscous liquid (0.64 g). Purification by flash chromatography with ethyl acetate/hexane 1:10 as eluent gave the product **28** as a viscous liquid in 49% yield (0.358 g). $[\alpha]_D^{22} = +8.5°$ ($c = 0.98$, $CHCl_3$); MS (CI, NH_3): $m/z = 637$ $[M+NH_4^+]$; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 145$, 133, 129.7, 127.9 (Ts), 103.2 (C-1), 78.0, 75.5, 73.7, 71.6 (C-2, C-3, C-4, C-5), 69.5, 67.9 (C-6, C-1′), 50.7 (C-2′), 21.5 (Ts), 1.1, 0.9, 0.6 (TMS); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.8$, 7.35 (2d, 4H, Ts), 4.29 (dd, 1H, H-6a, $J_{6a,6b} = 10.5$, $J_{6a,5} = 2$ Hz), 4.18 (d, H-1, $J_{1,2} = 7.5$ Hz), 4.00 (dd, 1H, H-6b, $J_{6b,5} = 7$ Hz), 3.83 (ddd, 1H, H-1′a, $J_{gem} = 11$, $J_{vic} = 6$, $J_{vic} = 4.5$ Hz), 3.36 (ddd, 1H, H-1′b, $J_{vic} = 6.5$, $J_{vic} = 4.5$ Hz), 3.42 (m, 3H, H-2′a, H-2′b, H-5), 3.39 (t, 1H, H-3, $J_{3,4}$, $J_{3,2} = 8.5$ Hz), 3.31 (dd, 1H, H-4, $J_{4,5} = 9$ Hz), 3.28 (dd, 1H, H-2), 2.4 (s, 3H, Ts), 0.2 (3s, 27H, TMS).

2-Azidoethyl 6-deoxy-6-iodo-2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranoside (29): To a solution of 2-azidoethyl 6-*O*-tosyl-2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranoside (**28**, 92 mg, 0.15 mmol) in dry DMF (1 mL) was added potassium iodide (300 mg, 1.5 mmol). After stirring at 80 °C for 1.5 h the mixture was cooled and partitioned between water (10 mL) and ethyl acetate (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organics were dried (Na_2SO_4) and concentrated to give **29** as a viscous liquid in ≈100% yield (85 mg). The product could be purified by flash chromatography with hexane/ethyl acetate 20:1 as eluent. $[\alpha]_D^{22} = +18.9°$ ($c = 1.25$, $CHCl_3$); MS (CI, NH_3): $m/z = 593$ $[M+NH_4^+]$; ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 103.4$ (C-1), 77.8, 75.9, 75.8, 75.3 (C-2, C-3, C-4, C-5), 68.0 (C-1′), 50.9 (C-2′), 6.8 (C-6), 1.2, 1.0, 0.96 (TMS); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 4.26$ (d, 1H, H-1, $J_{1,2} = 7.5$ Hz), 4.20 (ddd, 1H, H-1′a, $J_{gem} = 11$, $J_{vic} = 6$, $J_{vic} = 4.5$ Hz), 3.76 (ddd, 1H, H-1′b, $J_{vic} = 7$, $J_{vic} = 4.5$ Hz), 3.59 (ddd, 1H, H-2′a, $J_{gem} = 12.5$ Hz), 3.55 (dd, 1H, H-6a, $J_{6a,6b} = 10$, $J_{5,6a} = 2$ Hz), 3.49 (ddd, 1H, H-2′b), 3.43 (t, 1H, H-3, $J_{2,3}$, $J_{3,4} = 8.5$ Hz), 3.36 (dd, 1H, H-2), 3.28 (t, 1H, H-4, $J_{4,5} = 8.5$ Hz), 3.24 (dt, 1H, H-5), 3.11 (dd, 1H, H-6b), 0.2 (3s, 27H, TMS).

Methyl 2,3,4-tri-*O*-benzyl-6-cyclohexylamino-6-deoxy-α-D-glucopyranoside (30): To a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucoside (**15**, 72 mg, 0.17 mmol) in dry dichloromethane (1 mL) at 0 °C was added diisopropylethylamine (32 μL, 0.18 mmol) and trifluoromethanesulfonic anhydride (30 μL, 0.18 mmol). After stirring for 15 min, freshly distilled cyclohexylamine (21 μL, 0.18 mmol) was added. After stirring for 1 h at 0 °C another portion of cyclohexylamine (21 μL, 0.18 mmol) was added. Stirring was continued for another 3.5 h. The solvent was removed, solid sodium hydrogencarbonate and chloroform were added, and the mixture was stirred. Filtration and concentration gave a crude product that was purified by flash chromatography with hexane/ethyl acetate/triethylamine 40:20:3 as eluent. Compound **30** was isolated as a viscous liquid in 78% yield (67 mg), and 7% of the starting material was recovered. MS (CI, NH_3): $m/z = 546$ $[M+1]$; ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 138$, 128.3–127.4 (Ph), 97.8 (C-1), 81.9, 79.9, 79.4 (C-2, C-3, C-4), 75.6, 74.8, 73.2 ($3OCH_2Ph$), 69.6 (C-5), 56.4 (C-1′), 55.1 (OCH_3), 47.3 (C-6), 33.5, 33.2, 26.0, 24.9, 24.8 (C-2′, C-3′, C-4′, C-5′, C-6′); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 7.35$ (m, 15H, Ph), 5.02, 4.92, 4.86, 4.84, 4.71, 4.69 (6d, 6H, $3OCH_2Ph$, $J \approx 11$), 4.57 (d, 1H, H-1, $J_{1,2} = 3.5$ Hz), 4.01 (t, 1H, H-3, $J_{3,4}$, $J_{3,2} = 9.5$ Hz), 3.78 (ddd, 1H, H-5, $J_{5,4} = 9.5$, $J_{5,6b} = 6.5$, $J_{5,6a} = 2.5$ Hz), 3.51 (dd, 1H, H-2), 3.42 (t, 1H, H-4), 3.39 (s, 3H, OCH_3), 2.97 (dd, 1H, H-6a, $J_{6a,6b} = 12$ Hz), 2.69 (dd, 1H, H-6b), 2.37 (m, 1H, H-1′), 2.4–2.16 and 1.35–1.0 (2m, 10H).

2-Chloroethyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (32), method A: To a solution of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside[32,33] (**31**, 250 mg, 0.58 mmol) in 2-chloroethanol (1 mL) at 0 °C was added trifluoromethanesulfonic acid (2 μL). The mixture was then stirred at 100 °C for 1 h. After cooling, aqueous saturated $NaHCO_3$ and ethyl acetate were added. The aqueous layer was extracted once with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by flash

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chromatography with hexane/ethyl acetate 3:1 and 2:1 as eluent to give the product **32** as an anomeric mixture α/β 4:3 in 60% yield (178 mg).

Method B: To a solution of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**31**, 250 mg, 0.58 mmol) in 2-chloroethanol (1 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (105 µL, 0.58 mmol). The mixture was then stirred at 20 °C for 6 days, and aqueous saturated $NaHCO_3$ was added. The stirring was continued for 30 min. The aqueous layer was extracted with ethyl acetate three times, and the combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography as above. This gave the product **32** as an anomeric mixture, α/β 3:2, in 76% yield (226 mg). ^{13}C NMR ($CDCl_3$, 125.8 MHz, α): δ = 138.6, 138.1, 138.0, 128.3–127.5 (Ph), 97.2 (C-1), 81.6, 79.9, 77.1, 74.9 (C-2, C-3, C-4, C-5), 75.5, 73.2 ($3OCH_2Ph$), 68.1 (C-1′), 61.6 (C-6), 42.3 (C-2′); ^{13}C NMR ($CDCl_3$, 125.8 MHz, β): δ = 138.6, 138.1, 138.0, 128.3–127.5 (Ph), 103.7 (C-1), 84.2, 82.0, 77.2, 69.9 (C-2, C-3, C-4, C-5), 75.0, 74.8 ($3OCH_2Ph$), 71.1 (C-1), 61.8 (C-6), 42.3 (C-2′); ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.3 (m, Ph), 5.06–4.67 (OCH_2Ph), 4.81 (d, H-1 (α), $J_{1,2}$ = 3.5 Hz), 4.54 (d, H-1 (β), $J_{1,2}$ = 8 Hz), 4.19 (dd, J = 11, J = 5 Hz), 4.06 (t, H-3 (α), $J_{3,4}$, $J_{3,2}$ = 9 Hz), 3.91–3.62 (m), 3.41 (ddd, J = 10, J = 4.5, J = 3 Hz), 3.61 (t, J = 9 Hz), 3.56 (dd, H-2 (α)), 3.49 (dd, H-2 (β), $J_{2,3}$ = 9.5 Hz); anal. calcd. for $C_{29}H_{33}O_6Cl$: C 67.89, H 6.48, Cl 6.91; found: C 67.70, H 6.53, Cl 7.2.

2-Azidoethyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (33): To a suspension of 2-chloroethyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (**32**, 1.06 g, 2.1 mmol) and potassium iodide (0.74 g, 4.6 mmol) in dry DMF (10 mL) was added sodium azide (1.34 g, 20.7 mmol). The mixture was stirred at 110 °C for 1 h. To the cooled solution was added water (30 mL) and ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organics were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography with hexane/ethyl acetate 2:1 and 1:1 as eluent to give the product **33** as an anomeric mixture in 86% yield (0.92 g). These could be separated by careful chromatography to give 48% α and 36% β. **33α**: $[\alpha]_D^{22}$ = + 31.4° (c = 0.9, $CHCl_3$). **33β**: $[\alpha]_D^{22}$ = + 4.6° (c = 1.1, $CHCl_3$). MS (CI, NH_3): m/z = 537 [$M + NH_4^+$]; ^{13}C NMR ($CDCl_3$, 125.8 MHz, α): δ = 138, 128.3–127.3 (Ph), 97.2 (C-1), 81.4, 79.9, 77.2, 71.1 (C-2, C-3, C-4, C-5), 75.5, 74.8, 73.1 (OCH_2Ph), 66.4 (C-1′), 61.5 (C-6), 50.4 (C-2′); ^{13}C NMR ($CDCl_3$, β): δ = 138, 128.4–127.5 (Ph), 103.6 (C-1), 84.3, 82.2, 77.3, 75.6 (C-2, C-3, C-4, C-5), 75.1, 75.0, 74.9 (OCH_2Ph), 68.3 (C-1′), 61.9 (C-6), 50.9 (C-2′); ^1H NMR ($CDCl_3$, α): δ = 7.35 (m, 15H, Ph), 5.02, 4.93, 4.87, 4.82, 4.79, 4.78 (6d, 6H, $3OCH_2Ph$, $J \approx 11$), 4.76 (d, 1H, H-1, $J_{1,2}$ = 3 Hz), 4.07 (t, 1H, H-3, $J_{3,4}$, $J_{3,2}$ = 9.5 Hz), 3.82–3.72 (m, 4H), 3.6–3.54 (m, 3H), 3.50 (ddd, 1H, J = 13, J = 7, J = 4 Hz), 3.44 (ddd, 1H, J = 13, J = 7, J = 4 Hz), 1.9 (s, 1H, OH); ^1H NMR ($CDCl_3$, β): δ = 7.35 (m, 15H, Ph), 4.97, 4.96, 4.89, 4.84, 4.76, 4.66 (6d, 6H, $3OCH_2Ph$, $J \approx 11$), 4.50 (d, 1H, H-1, $J_{1,2}$ = 7.5 Hz), 4.05 (ddd, 1H, J = 10.5, J = 6, J = 4 Hz), 3.89 (dd, 1H, J = 12, J = 2.5 Hz), 3.76 (ddd, 1H, J = 10.5, J = 6, J = 4 Hz), 3.75 (dd, 1H, J = 12.5, J = 4 Hz), 3.70 (t, 1H, H-3, $J_{3,4}$, $J_{3,2}$ = 9 Hz), 3.61 (t, 1H, H-4, $J_{4,5}$ = 9 Hz), 3.48 (dd, 1H, H-2), 3.47 (m, 1H), 3.39 (ddd, 1H, J = 10, J = 4.5, J = 3 Hz), 1.9 (s, 1H, OH); anal. calcd. for $C_{29}H_{33}N_3O_6$: C 67.04, H 6.40, N 8.09; found: C 66.83, H 6.61, N 8.03.

2-Azidoethyl 2,3,4-tri-*O*-benzyl-6-*O*-triflate-α-D-glucopyranoside (34): To a solution of 2-azidoethyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**33**, 143 mg, 0.28 mmol) and diisopropylethylamine (50 µL, 0.29 mmol) in dry dichloromethane (3 mL) at 0 °C was added trifluoromethanesulfonic anhydride (48 µL, 0.29 mmol). After stirring for 30 min at 0 °C under an argon atmosphere the triflate was used in situ.

2-Azidoethyl 6-amino-2,3,4-tri-*O*-benzyl-6-deoxy-6-*N*-[(3*R*,4*R*)-3,4-dibenzyloxy-5-benzyloxymethylcyclohex-5-enyl]-α-D-glucopyranoside (35): To a solution of amine hydrochloride **22** (140 mg, 0.30 mmol) in dry nitromethane was added Amberlite ion-exchange resin IR 67 OH^- (≈2.5 mL) in nitromethane (1 mL). The Amberlite had been thoroughly prewashed with methanol followed by nitromethane. After stirring for 30 min under an argon atmosphere, the free amine was quickly filtered directly into a solution of the triflate **34** (0.28 mmol), prepared as described above. Diisopropylethylamine (50 mL) was added, and stirring was continued for 1 h at 0 °C and then for 4 h at 20 °C. The solvents were removed, and the residue was partitioned between ethyl acetate and aqueous saturated $NaHCO_3$. The aqueous layer was extracted three times with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated (0.27 g). Purification by flash chromatography with hexane/ethyl acetate 2:1 and 1:1 gave product **35** in 78% yield (180 mg). $[\alpha]_D^{22}$ = +19.5° (c = 2.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$, 125.8 MHz, pH 7): δ = 138, 128.2–127.3 (Ph), 132 (C-6′), 97.0 (C-1), 81.5 (C-3), 79.9, 78.8 (C-2, C-4), 75.4, 74.7, 73.2, 72.9, 71.1, 70.7 ($6OCH_2Ph$), 74.4 (C-3′, 74.3 (C-4′), 71.5 (C-7′), 70.5 (C-5), 66.2 (C-1″), 50.4 (C-2″), 50.2 (C-1′), 47.0 (C-6), 30.2 (C-2′); ^1H NMR ($CDCl_3$, 500 MHz, pH 7): δ = 7.3 (m, 30H, Ph), 5.95 (s, 1H, H-6′), 5.01, 4.92, 4.85, 4.82, 4.70, 4.67, 4.66, 4.64, 4.57, 4.53, 4.40 (12d, 12H, $6OCH_2Ph$, $J \approx$ 11–12 Hz), 4.73 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.22 (d, 1H, H-7′a, $J_{7'a,7'b}$ = 11.5 Hz), 4.05 (t, 1H, H-3, $J_{3,4}$, $J_{3,2}$ = 9.5 Hz), 4.00 (d, 1H, H-4′, $J_{4',3'}$ = 3.5 Hz), 3.91 (m, 1H, H-3′), 3.98 (d, 1H, H-7′b), 3.83 (m, 2H, H-5, H-1″a), 3.7–3.5 (m, 2H, H-4, H-1″b), 3.53 (dd, 1H, H-2, $J_{2,3}$ = 9.5 Hz), 3.48 (m, 2H, H-2′a, H-2′b), 3.41 (m, 1H, H-1′), 2.98 (dd, 1H, H-6a, $J_{6a,6b}$ = 12, $J_{6a,5}$ = 2 Hz), 2.79 (m, 1H, H-6, $J_{6b,5}$ = 6 Hz), 2.11 (dt, 1H, H-2′$_{eq}$, $J_{2'eq,2'ax}$ = 13, $J_{2'eq,3}$, $J_{2'eq,1}$ = 5.5 Hz), 1.74 (ddd, 1H, H-2′$_{ax}$, $J_{2'ax,3}$ = 8.5, $J_{2'ax,1}$ = 2 Hz).

6-Amino-6-deoxy-6-*N*-[(1*R*,3*R*,4*R*)-3,4-dihydroxy-5-hydroxymethylcyclohex-5-enyl]-α-D-glucopyranose (4): To a solution of **35** (48 mg, 58 mmol) in dry THF (1.5 mL) under argon and at −78 °C was added liquid ammonia (≈15 mL), followed by small sodium pieces (40 mg). The blue reaction mixture was stirred at −78 °C for 3 h, and water (3 mL) was added. The ammonia was evaporated by a stream of argon, and the solvents were removed on the rotary evaporator. The residue was dissolved in a small amount of water and eluted through a column of CG 50 ion-exchange resin (10 mL) with water. Concentration of the first fractions gave the title compound **4** as an anomeric mixture in quantitative yield (23 mg). $[\alpha]_D^{22}$ = +11° (c = 1.1, H_2O); ^{13}C NMR (D_2O, 125.8 MHz, pH 7): δ = 144.5, 144.4 (C-5), 118.8 (C-6′), 96.8 (C-1 (β)), 92.9 (H-1 (α)), 76.2, 74.7, 72.5, 72.2, 72.2, 72.1, 69.1, 67.9, 67.85, 67.7, 62.9, 62.4, 52.8, 52.5 (C-1′), 46.4, 46.3 (C-6), 28.7, 28.0 (C-2′); ^1H NMR (D_2O, 500 MHz, pH 7): δ = 5.89 (s, H-6′), 5.21 (d, H-1 (α), J = 3.5 Hz), 4.64 (d, H-1 (β), J = 7.5 Hz), 4.18 (s), 4.07–4.02 (m), 3.94 (d, J = 3 Hz), 3.68 (ddd, J = 17, J = 6, J = 2 Hz), 3.58 (m), 3.54 (dd, J = 10, J = 3 Hz), 3.49 (m), 3.47 (t, J = 9 Hz), 3.32 (t, J = 9.5 Hz), 3.31 (m), 3.26 (t, J = 9 Hz), 3.24 (m), 2.21 (m, H-2′$_{eq}$), 2.20 (m, H-2′$_{ax}$).

Measurements of glycohydrolase inhibition: Each glycosidase assay was performed by preparing eight 2 mL samples in cuvettes consisting of 1 mL sodium phosphate buffer (0.1 M) of either pH 6.8 or 7.5, 0.2 to 0.8 mL of a 5 or 10 mM solution of either 4-nitrophenyl α-D-glucopyranoside, 4-nitrophenyl β-D-glucopyranoside, 4-nitrophenyl α-L-fucopyranoside or 2-nitrophenyl β-D-galactopyranoside in water, 0.1 mL of a solution of either the potential inhibitor (**4** or **5**) or water, and distilled water to a total volume of 1.9 mL. Four of the samples contained the potential inhibitor at a fixed concentration but with variant nitrophenyl glycoside concentration. The other four samples contained no inhibitor, but also variant nitrophenyl glycoside concentration. Finaly the reaction was started by adding 0.1 mL of a dilute solution of either α-glucosidase from bakers' yeast (EC 3.2.1.20, Sigma G-5003), β-glucosidase from almonds (EC 3.2.1.21, Sigma G-0395), α-mannosidase from jack beans (Sigma) or isomaltase from bakers' yeast (Sigma), and the formation of 4-nitrophenol was followed for 2 to 10 min at 22–27 °C by measuring absorbance at 400 nm. Initial velocities were calculated from the slopes for each of the eight reactions and used to construct two Hanes plots, one for the mixture with and one for that without inhibitor. From the two Michaelis–Menten constants (K_m) thus obtained the inhibition constant (K_i) was calculated. Glycogen phosphorylase inhibition was measured as described by Johnson.[43]

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