Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2259–2271

TETRAHEDRON

Synthesis of novel HIV-1 protease inhibitors based on carbohydrate scaffolds

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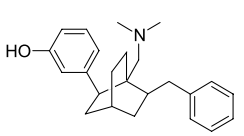
Received 30 October 2002; revised 22 January 2003; accepted 7 February 2003

Abstract—The synthesis of peptidomimetic inhibitors of HIV-1 protease based on 6-deoxy-6-amino-β-D-glucopyranoside and 6-deoxy-6-amino-β-D-mannopyranoside scaffolds has been achieved. The inhibitors had IC_{50} values in the micromolar range. The results provide a platform for the development of more potent carbohydrate based inhibitors of HIV-1 and other aspartic proteases.

1. Introduction

The aspartic acid proteases are an important class of enzymes, which catalyse sequence selective amide hydrolysis.[1] These enzymes employ a bound water molecule as a nucleophile that attacks the amide carbonyl of the bond to be cleaved. The water molecule is activated by aspartic acid residues contained at the active site. The active site also consists of binding subsites, which recognise the substrate residues and permit selectivity. Several aspartic acid proteases are of interest as therapeutic targets. Examples include renin, HIV-1 protease and memapsin 2 (β-secretase) which are, respectively, involved in hypertension,[2] viral infection and Alzheimer's disease.[3] Only in the case of the HIV-1 protease have inhibitors of this class of enzymes attained clinical importance.[4] This is due mostly to the lack of bioavailability of the potent inhibitors, which is caused in many cases by the high peptide character of these compounds. Also, despite the successes of using protease inhibitors for treatment of HIV, there remain a number of problems with current therapies. A major problem with the existing HIV protease inhibitors is that of adverse side effects. The most frequently reported effects are gastrointestinal complaints, nausea, diarrhoea, fat redistribution, anorexia and neurological disturbances.[5] HIV is characterised by a high turnover rate and poor reverse-transcriptase fidelity,[6] which leads to mutations in the protease enzyme. These mutations may be fatal to the virus, have no effect, or confer either increased or decreased susceptibility to antiretroviral agents. The latter leads to the problem of overlapping resistance patterns. In addition, it has been found that, even in patients with undetectable viral levels, a population of viruses remain in 'reservoir cells' beyond the reach of existing antiviral drugs.[7] Consequently much work is being carried out to develop new anti-HIV agents, including the screening of natural products.[8]



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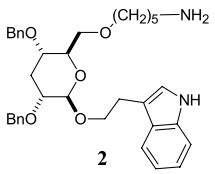

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Peptidomimetic research, which has the ultimate goal of developing inhibitors with improved pharmacokinetic properties,[9] has led to a move beyond the traditional approach of replacing the scissile bond of a peptide substrate with a non-cleavable isostere. Instead the pharmacophoric groups are placed on a non-peptide scaffold, which can orient them in the direction of their respective binding subsites. In 1980 Farmer proposed, though did not explore, the use of cyclohexane as such a scaffold.[10] In 1986, following the discovery of the enkephalins, Belanger and Dufresne designed target **1** using a bicyclooctane scaffold.[11] This is the first non-peptide peptidomimetic with novel scaffolding, which is recognised by the opiate receptor for which it was designed. Researchers at the University of Pennsylvania introduced the use of β-D-glucopyranose (e.g. **2**), its enantiomers and a diastereomer (β-D-mannopyranose) as scaffolds for the design and synthesis of ligands for the somatostatin (SRIF), the substance P (SP), and the β_2-adrenergic receptors.[12] Although initially the affinities were

Keywords: HIV-1; inhibitors; aspartic acid; carbohydrate based peptidomimetics.

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0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00208-4

modest (15 μM range), more potent ligands have been designed, synthesized and reported subsequently.[13] Concurrent with the early Penn studies, Olson and co-workers at Hoffmann LaRoche reported a conceptually similar approach with the synthesis of a thyrotropin-releasing hormone mimic, which employed a cyclohexane scaffold.[14] Validation of the concept led other groups to utilize sugar scaffolds in peptidomimetic and other research.[15,16] The results clearly indicate that screening libraries based on the privileged carbohydrate scaffolds[17] hold great promise for being universally useful as drug discovery platforms. In a recent communication we reported the design, synthesis, and evaluation of first generation peptidomimetic inhibitors of HIV-1 protease that incorporate a β-D-mannopyranoside scaffold; we now provide a full account of this work.[18]

2. Results and discussion

2.1. Design of carbohydrate based inhibitors of HIV-1 protease

The design of the carbohydrate based peptidomimetics was structure based and included the use of the 3D structure of inhibitor **3** bound to HIV-1 protease.[19] The de novo software Growmol,[20,21] which explores the generation of a diverse range of molecules complementary to the binding site of enzymes, was initially used as a tool to aid the structure based design process. This generated a cyclohexane derivative **4** in the aspartic protease active site. This cyclohexane was superimposed on **3**; this led to the suggestion of using carbohydrate based scaffolds related to **6** and **7** as replacements for part of the peptide structures known to bind to these enzymes. It was apparent that β-D-mannopyranoside could be a suitable scaffold. A substituent attached at C-1, aided by the *exo*-anomeric effect, would be projected with the correct orientation into the S_1 subsite. Functionalisation of the 3-OH and 4-OH would possibly place groups into the S_1' and S_2 subsites. A 6-deoxy-6-amino glycoside could be used for the synthesis of amide derivatives, which would be useful for introducing further diversity and the amide group would be capable of hydrogen bonding with residues of the enzyme. Many inhibitors of aspartic proteases, including **3**, as well as those that are clinically used for HIV infection and the naturally occurring aspartic protease inhibitor pepstatin, contain the hydroxyethylene isostere. It is accepted that the interaction of the isosteric hydroxyl group with the enzyme is one of the most important forces for complex stability; the correct stereochemistry of this hydroxyl is usually essential for tight binding and it has been suggested that when designing inhibitors of aspartic acid proteases it is valuable to synthesise both hydroxyl isomers.[1,22] In this case the 2-OH group of the mannose scaffold had the desired overlap with the hydroxyl group of inhibitor **3**; we also considered the synthesis of compounds based on the other isomer, that is the more accessible β-D-glucopyranoside. The three dimensional structures of other HIV-1 protease–ligand complexes led us to suggest compounds of general structure **6**[23] and related compounds as preliminary synthetic targets. We also wanted to consider synthesis of the conformationally restrained carbohydrates structurally related to **7** for biological evaluation (Fig. 1).

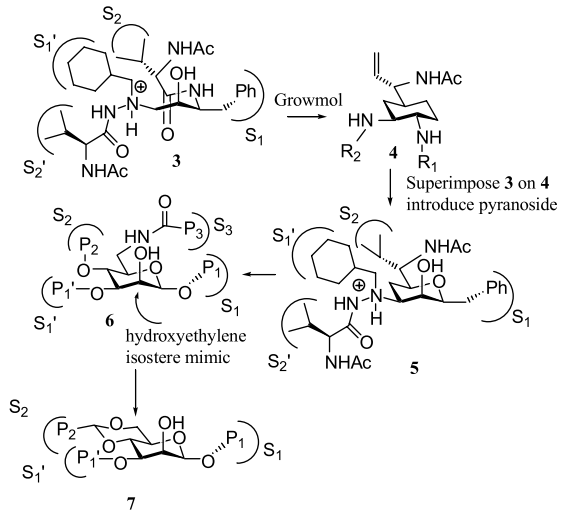
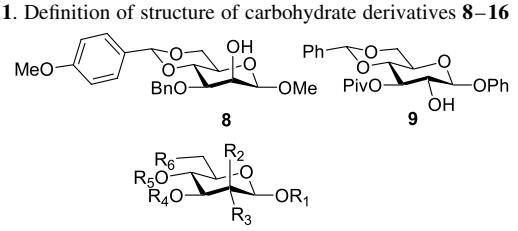


Figure 1. Design of β-D-mannopyranoside based HIV-protease inhibitors. Inhibitor **3** is shown in its enzyme bound conformation.

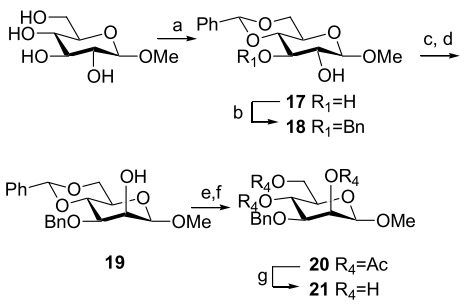
2.2. Synthesis and biological evaluation of carbohydrate based inhibitors

The synthesis of structures related to **6** and **7** (**8**–**16**; Table 1) was thus carried out. Methyl-β-D-glucopyranoside was converted to the benzylidene derivative **17** (80%) when reacted with benzaldehyde dimethyl acetal in the presence of camphorsulfonic acid in acetonitrile. Regioselective benzylation of **17** using dibutyltin oxide, tetrabutylammonium iodide and benzyl bromide gave **18** in 85% yield. This was converted into the mannose derivative **19** by first oxidising to the ketone using dimethyl sulfoxide and acetic anhydride (1:2), followed by reduction using sodium borohydride (34%).[24] The benzylidene group was then removed from **19** using a 30% trifluoroacetic acid (TFA) solution in dichloromethane; however upon concentration to remove the TFA, the benzylidene group was re-introduced and it was necessary to overcome this reaction by adding Ac_2O/pyridine to the reaction mixture containing the triol **21** to give **20**. The pure triol **21** was thus obtained (75%) after deacetylation of **20** using NaOMe/MeOH (Scheme 1).

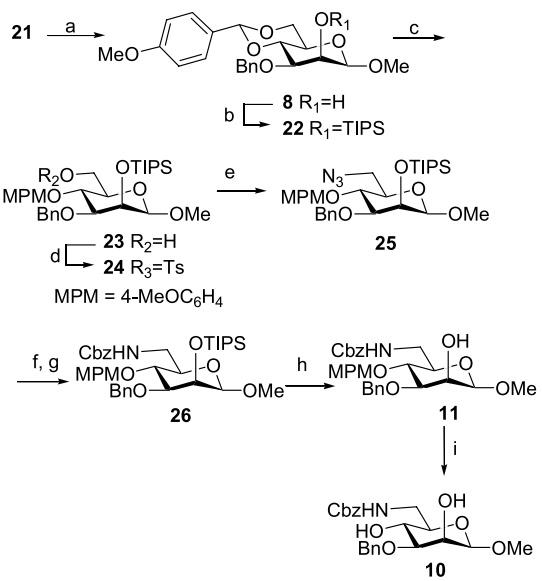
Table 1. Definition of structure of carbohydrate derivatives **8**–**16**



Comp.	R_1	R_2	R_3	R_4	R_5	R_6
10	Me	OH	H	Bn	H	NHCbz
11	Me	OH	H	Bn	MPM	NHCbz
12	Me	OH	H	Bn	MPM	NHAc
13	Me	H	OH	H	H	NHBoc
14	Me	H	OH	Bn	H	NHAc
15	Ph	H	OH	Piv	H	OPiv
16	Ph	H	OH	H	H	NHAc

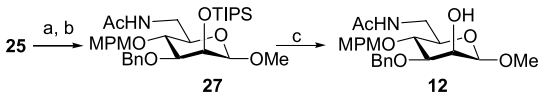


Scheme 1. *Reagents and conditions*: (a) $PhCH(OMe)_2$, CSA, MeCN, 80%; (b) Bu_2SnO, BnBr, Bu_4NI, 85%; (c) DMSO, Ac_2O (1:2), rt; (d) $NaBH_4$, CH_2Cl_2, silica gel, rt, 33% for two steps (mannose/glucose ratio, 7:1); (e) TFA, CH_2Cl_2, rt; (f) Ac_2O, Py, rt; (g) NaOMe, MeOH, rt, 75% for three steps.

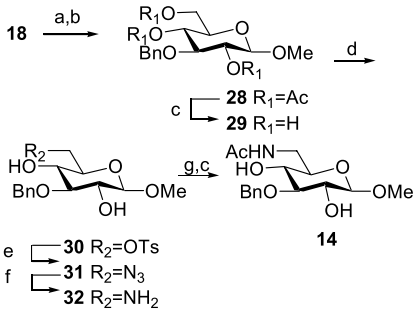


Scheme 2. *Reagents and conditions*: (a) $4\text{-}MeOC_6H_4CH(OMe)_2$, CSA, MeCN, 76%; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (c) DIBAL-H, CH_2Cl_2 89% for two steps; (d) TsCl, Py, 0°C, 60%; (e) NaN_3, DMF, 80°C, 79%; (f) Lindlar catalyst, H_2, EtOH/EtOAc; (g) BnOCOCl, THF/H_2O, 22% for two steps; (h) TBAF, THF, 0°C, 82%; (i) DDQ, CH_2Cl_2/H_2O (10:1), 0°C, 81%.

The 4-methoxybenzylidene derivative **8** was next prepared (76%, Scheme 2) by the reaction of **21** with 4-methoxybenzaldehyde dimethyl acetal in the presence of camphorsulfonic acid. Protection of the 2-OH with triisopropylsilyl triflate (TIPSOTf) in the presence of 2,6-lutidine in dichloromethane gave **22**. It was difficult to separate the by-product, triisopropylsilyl alcohol (TIPSOH) from the product by chromatography as they had the same mobility on silica. Fortunately the presence of the TIPSOH had no adverse effect on the subsequent regiospecific reduction of the acetal **22**, which gave **23** (89% after two steps) after treatment with DIBAL-H in dichloromethane; the TIPSOH was easily removed by chromatography at this stage. Alcohol **23** was then converted in turn to the tosylate **24** (60%) and to the azide **25**. The azide was subsequently reduced using the Lindlar catalyst and hydrogen to give the amine (75% over 2 steps). The intermediate amine was next reacted with benzyl chloroformate in aqueous THF to give the carbamate **26** (22% for two steps). Sequential removal of the TIPS group using tetrabutylammonium fluoride (TBAF)



Scheme 3. *Reagents and conditions*: (a) Lindlar catalyst, H_2, EtOH/EtOAc; (b) Ac_2O, Py, rt, 88% for two steps; (c) TBAF, THF, 0°C, 98%.



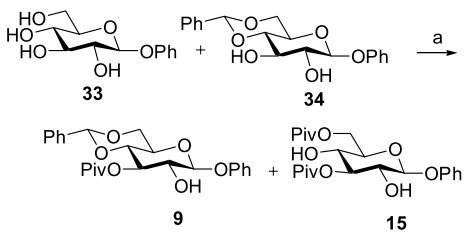
Scheme 4. *Reagents and conditions*: (a) TFA, CH_2Cl_2, rt; (b) Ac_2O, Py, rt, 90% for two steps; (c) NaOMe, MeOH, rt, 100%; (d) TsCl, Py, 0°C; (e) NaN_3, DMF, 80°C; (f) PPh_3, Et_2O, then H_2O; (g) Ac_2O, Py, rt, 25% for four steps.

in THF provided **11** (82%) and the 4-methoxybenzyl group of **11** oxidatively with DDQ in aqueous dichloromethane provided the desired target compound **10** in an 81% yield (Scheme 2).

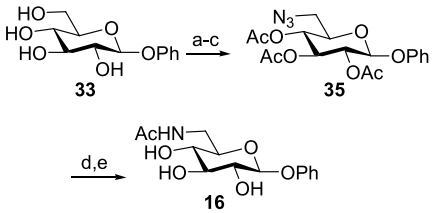
The acetylation of the amine, obtained from reduction of **25**, to give **27** (88%) followed by TBAF mediated removal of the TIPS group gave **12** in 98% yield (Scheme 3).

The triol **29**[25] was prepared from **18** by a sequence similar to that used in the synthesis of **21** (Scheme 4). This intermediate was converted to the azide **31**, in two steps. Reduction (PPh_3 and H_2O) followed by acetylation and deprotection gave **14** in quantitative yield.

Phenyl β-D-glucopyranoside **33** was used for the synthesis of **9**, **15** (Scheme 5) and **16** (Scheme 6). The reaction of **33** with benzylidene dimethyl acetal in presence of camphorsulfonic acid in acetonitrile gave a mixture of recovered **33**



Scheme 5. *Reagents and conditions*: (a) $(CH_3)_3COCl$, Py, rt.



Scheme 6. *Reagents and conditions*: (a) TsCl, Py, 0°C; (b) NaN_3, DMF, 80°C; (c) Ac_2O, Py, rt, 34% for three steps; (d) PPh_3, Et_2O, then H_2O; (e) NaOMe, MeOH, rt.

Table 2. HIV-1 Protease inhibition data for carbohydrates

Compd.	Inhibition (IC_{50}, μM)[a]
8	4.85 (±1.63)
9	3.81 (±1.11)
10	4.66 (±2.21)
11	4.48 (±0.98)
12	7.74 (±3.19)
13	Not active
14	5.06 (±0.61)
15	3.97 (±1.00)
16	8.95 (±1.48)

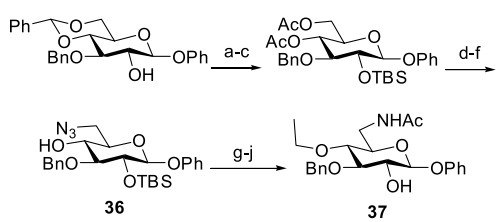
Inhibitory values for clinically used indinavir, saquinavir and nelfinavir in this assay are 0.37, 0.27 and 0.53 nM, respectively.

[a] Values are means of two experiments, standard deviation is given in parentheses.

and product **34**; when this mixture was treated with trimethylacetyl chloride in the presence of pyridine,[26] both **9** and **15** were obtained. These compounds and the related congeners shown in Table 1 have been evaluated in an HIV-1 protease inhibition assay.[27] The biological data is summarised in Table 2.

Most of the compounds evaluated displayed moderate inhibition (IC_{50}, 3.81–8.95 μM) whereas **13** was inactive. Clearly further optimization of binding to the enzyme is required. It is most likely for compounds **8** and **10**–**14** that the P_1 substituent is too small; the activity displayed by **9**, **15** and **16** and lack of activity of **13** indicate that it may be desirable to have larger groups such as the phenyl group for saccharide based inhibitors. Molecular modelling using 3D structures of the HIV-protease did indicate that the methoxyphenyl group in **8**, **11** and **12** and the phenyl group in **9** could have steric interactions with residues in the S_2 subsite. However, large conformational changes have been observed in HIV-1 protease in response to large groups on inhibitors and it has been suggested before that attempts can be made to probe protein flexibility during inhibitor development.[1,28] The inhibitory values for **9** and **14**–**16** indicate that the synthetically more accessible β-D-glucopyranosides are relevant scaffolds and should be considered in inhibitor development. It is encouraging that compounds that can be prepared in one or two steps, namely **9** and **15**, are active. This observation should facilitate rapid preparation of compound libraries for evaluation as inhibitors.

In view of the preliminary results, we are now in the process of preparing a second generation of prospective HIV inhibitors. The synthesis of **37** has been carried out (Scheme 7). This illustrates that introduction of diverse groups at the C-4 and C-6 positions of the carbohydrate scaffold, as part



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Scheme 7. *Reagents and conditions*: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2; (b) TFA, CH_2Cl_2, rt; (c) Ac_2O, Py, rt, 48% for two steps; (d) NaOMe, MeOH, rt; (e) TsCl, Py, 0°C, 66% for 2 steps; (f) NaN_3, DMF, 80°C, 90%; (g) NaH, EtI, THF, 0°C to rt, 82%; (h) Lindlar catalyst, H_2, EtOH/EtOAc (10:1); (i) Ac_2O, Py, rt, 86% for two steps; (j) TBAF, THF, 0°C, 97%.

of the optimization of binding to the enzyme, should be amenable from intermediate **36**. It should also be possible to adapt this synthetic strategy to the solid phase if a linker incorporating a silicon based protecting group were to be used to protect the C-2 hydroxyl group.

3. Summary

In summary, a series of β-D-manno- and β-D-glucopyranosides have been synthesised that show modest inhibitory activity for the HIV-1 protease. Importantly these preliminary results provide a basis for the development of more potent carbohydrate based peptidomimetic inhibitors of aspartic proteases. Work is currently underway to optimise the binding of a variety of saccharide derivatives to these enzymes and to develop further the synthetic route for application on the solid phase. In addition, it seems worthwhile to evaluate these and related structures as inhibitors of the other aspartic acid proteases, since all enzymes from this class bind their substrates/inhibitors in extended β-sheet conformations and utilise similar modes of binding between the substrate/inhibitor and the enzyme.[29]

4. Experimental

4.1. General

Optical rotations were determined with a Perkin–Elmer 241 model polarimeter at the sodium D line at 23°C. NMR spectra were recorded with JEOL JNM-GX270, Varian Inova 300, and Bruker AM500 spectrometers. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ, 0.0), HOD for D_2O (δ 4.63) or Me_2SO-d_6 (δ 2.50) (δ 2.20) for ^1H and either $CDCl_3$ (δ 77.0) or Me_2SO-d_6 (δ 43.5) for ^{13}C. Coupling constants are reported in hertz. IR spectra were recorded with a Mattson Galaxy Series FTIR 3000 using either thin film between NaCl plates or KBr discs, as specified. Melting points were measured on a Gallenkamp melting point apparatus. Elemental analysis was performed on an Exeter Analytical CE440 elemental analyser. Low and high resolution mass spectra were measured on either a micromass VG 70/70H or VG ZAB-E or autospec spectrometers and were measured in ES positive mode unless otherwise indicated. TLC was performed on aluminium sheets precoated with Silica Gel 60 (HF_{254}, E. Merck) and spots visualized by UV and charring with H_2SO_4/EtOH (1:20). Flash Column Chromatography was carried out with Silica Gel 60 (0.040–0.630 mm, E. Merck) and using a stepwise solvent polarity gradient correlated with TLC mobility. Chromatography solvents used were EtOAc (Riedel–deHaen), MeOH (Riedel–deHaen) and petroleum ether (b.p. 40–60°C, BDH laboratory supplies). Acetonitrile, benzene and CH_2Cl_2 reaction solvents were freshly distilled from calcium hydride and anhydrous DMF was used as purchased from Sigma–Aldrich. Methyl and phenyl β-D-glucopyranosides were purchased from Sigma–Aldrich.

4.1.1. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (17). A solution of methyl β-D-glucopyranoside (10 g,

49 mmol), camphorsulfonic acid (50 mg) and benzaldehyde dimethylacetal (14.8 mL, 78.8 mmol) in MeCN (400 mL) was stirred for 12 h at room temperature. Triethylamine (5 mL) was added and the solution was allowed to stir for a further 1 h. The product was then filtered off as a white solid, washed with petroleum ether and dried under diminished pressure (**17**); mp 169–172°C; $[\alpha]_D=-61.5$ (*c* 0.2, $CHCl_3$) (lit.:[30] mp 198–200°C; $[\alpha]_D=-65.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.26 (overlapping signals, 5H, aromatic H), 5.55 (s, 1H, C*H*Ph), 4.36 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=10.5$ Hz, H-6a), 4.33 (d, 1H, $J_{1,2}=8.0$ Hz, H-1), 3.82 (apt t, 1H, $J_{2,3}=9.0$ Hz, $J_{3,4}=9.0$ Hz, H-3), 3.80 (apt t, 1H, $J_{5,6b}=10.5$ Hz, H-6b), 3.59 (s, 3H, OCH_3), 3.48 (overlapping signals, 3H, H-2,4,5); ^{13}C NMR (Me_2SO-d_6/$CDCl_3$, 1:10): δ 137.5 (s, aromatic C), 129.2, 128.2, 126.6 (each d, each aromatic CH), 104.6, 101.9, 80.6, 74.9, 73.6 (each d), 68.9 (t, C-6), 66.5 (d), 57.4 (q, OCH_3); IR (KBr): 3385, 3241, 2981, 2942, 2882, 1452, 1388, 1227, 1087, 1038, 997, 694 cm^{-1}.

4.1.2. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (18). Compound **17** (8.0 g, 28.4 mmol) and dibutyltin oxide (8.41 g, 34.6 mmol) were dissolved in benzene (400 mL) and stirred for 16 h, with azeotropic removal of water. The solution was then concentrated to 200 mL and benzyl bromide (7.81 mL, 30.4 mmol) and tetrabutylammonium iodide (11.85 g, 32.1 mmol) were added and it was again allowed to stir, heating at reflux, for a further 16 h. The solution was then concentrated and the resulting yellow solid recrystallised from MeOH to give **18** as a white solid (8.4 g, 85%); mp 119–121°C (MeOH). The ^1H and ^{13}C NMR data are identical with those previously reported.[31] ES-HRMS: Found 373.1654, required 373.1651 $[M+H]^+$.

4.1.3. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside (19). Glucose derivative **18** (30.0 g) was dissolved in dimethyl sulfoxide and acetic anhydride (1:2, 1.38 L) and stirred for 16 h. Water (500 mL) was then added and the product was extracted into Et_2O (3×300 mL). The organic layer was then carefully washed several times with aq. $NaHCO_3$, dried and the residue was adsorbed onto silica (100 g); chromatography was used to separate unreacted **18** and a by-product, the methylthiomethyl ether from the ketone (10.5 g, 34%). The ^1H and ^{13}C NMR data of the ketone was identical with that previously reported.[32] Sodium borohydride (5.9 g, 0.16 mol) was then added slowly to a cooled (0°C) mixture of **11** (10.5 g, 30.3 mmol) and silica (10 g) in $MeOH/CH_2Cl_2$ (1:1, 250 mL). After 30 min the mixture was allowed to warm to room temperature and was stirred for 12 h. The residue was purified by chromatography to give **18** (1.07 g, 10.2%) and **19** (8.7 g, 87.0%). The ^1H- and ^{13}C NMR data for **19** are identical with data that have been previously reported.[31]

4.1.4. Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-mannopyranoside (20). To a solution of **19** (8.7 g, 25 mmol) in CH_2Cl_2/H_2O (50:1, 50 mL) was added trifluoroacetic acid (30 mL of 30% CH_2Cl_2 solution). After stirring for 30 min. pyridine (100 mL) was added, followed by acetic anhydride (100 mL). The solution was allowed to stand overnight and the solvent was then removed and the residue purified by chromatography to provide **20** (7.5 g, 75%); $[\alpha]_D=-84.8$ (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.24 (overlapping signals, 5H, aromatic H), 5.60 (dd, 1H, $J_{1,2}=1.0$ Hz, $J_{2,3}=3.5$ Hz, H-2), 5.22 (apt t, 1H, $J_{3,4}=10.0$ Hz, $J_{4,5}=10.0$ Hz, H-4), 4.56 (AB d, 2H, $J=13.0$ Hz, OCH_2Ph), 4.43 (d, 1H, H-1), 4.27 (dd, 1H, $J_{5,6a}=5.5$ Hz, $J_{6a,6b}=12.5$ Hz, H-6a), 4.15 (dd, 1H, $J_{5,6b}=2.5$ Hz, H-6b), 3.56 (dd, 1H, H-3), 3.56 (ddd, 1H, H-5), 3.52 (s, 3H, OCH_3), 2.18, 2.07, 2.02 (each s, each 3H, CH_3, (OAc)); ^{13}C NMR ($CDCl_3$): δ 170.8, 170.6, 169.6 (each s, each C=O), 137.4 (s, aromatic C), 128.5, 128.0, 127.9 (each d, each aromatic CH), 100.1 (d, C-1), 76.5, 72.5 (each d), 71.1 (t), 67.6, 67.3 (each d), 62.8 (t), 57.3 (q, OCH_3), 21.0, 20.8, 20.8 (each q, OAc); IR (KBr): 2964, 2876, 1745, 1453, 1371, 1233, 1096, 1056, 755, 700, 624 cm^{-1}; CI-HRMS: Found 428.1917, required 428.1921 $[M+NH_4]^+$.

4.1.5. Methyl 3-*O*-benzyl-β-D-mannopyranoside (21). The acetylated derivative **20** (7.3 g, 17.8 mmol) was dissolved in methanol and elemental sodium (0.1 g) was added. The solution was stirred and formation of an intermediate was observed after 30 min; it took a further 48 h for the acetate groups to be removed from this intermediate. Amberlite IR-120 (plus) ion exchange resin was then added and the solution was stirred for 10 min. It was then filtered and concentrated to give **21** as a pale oil (5.1 g, quantitative); $[\alpha]_D=-63.7$ (*c* 0.35, MeOH); ^1H NMR (300 MHz, $CDCl_3/Me_2SO$-d_6; 10:1): δ 7.41–7.27 (overlapping signals, 5H, aromatic H), 4.72 (AB d, 2H, $J=12.0$ Hz, OCH_2Ph), 4.33 (d, 1H, $J_{1,2}=1.0$ Hz, H-1), 4.05 (dd, 1H, $J_{2,3}=3.0$ Hz, H-2), 3.96 (apt t, 1H, $J_{3,4}=9.5$ Hz, $J_{4,5}=9.5$ Hz, H-4), 3.86 (overlapping signals, 2H, H-6a, H-6b), 3.53 (s, 3H, OCH_3), 3.37 (dd, 1H, H-3), 3.56 (apt dt, 1H, $J_{5,6a}=4.0$ Hz, $J_{5,6b}=4.0$ Hz, H-5); ^{13}C NMR ($CDCl_3/Me_2SO$-d_6; 10:1): δ 138.3 (s, aromatic C), 128.6, 128.1, 128.0 (each d, each aromatic CH), 101.5 (d, C-1), 81.2, 77.9 (each d), 71.6 (t), 68.2, 66.8 (each d), 62.3 (t), 57.2 (q, OCH_3); IR (KBr): 3432, 2940, 1635, 1454, 1373, 1214, 1062, 882, 711 cm^{-1}; ES-HRMS: Found 307.1155, required 307.1158 $[M+Na]^+$.

4.1.6. Methyl-3-*O*-benzyl-4,6-*O*-(4-methoxy-benzylidene)-β-D-mannopyranoside (8). The triol **21** (3 g, 10.8 mmol), camphorsulphonic acid (60 mg) and 4-methoxy benzaldehyde dimethylacetal (6.0 mL, 21.6 mmol) in MeCN (60 mL) were stirred for 10 min at room temperature. Triethylamine (0.06 mL) was added and the solution was stirred for a further 10 min., then concentrated and the product was purified by chromatography to give **8** as a white solid (3.3 g, 76%); $[\alpha]_D=-27.2$ (*c* 0.36, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.44–6.89 (overlapping signals, 9H, aromatic H), 5.56 (s, 1H), 4.81 (AB d, 2H, $J=12.5$ Hz, OCH_2Ph), 4.42 (d, 1H, $J_{1,2}=1.0$ Hz, H-1), 4.32 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=10.5$ Hz, H-6a), 4.12 (apt t, 1H, $J_{3,4}=9.5$ Hz, $J_{4,5}=9.5$ Hz, H-4), 4.11 (dd, 1H, $J_{2,3}=2.5$ Hz, H-2), 3.87 (apt t, 1H, $J=10.5$ Hz, H-6b), 3.81 (s, 3H, OMe), 3.64 (dd, 1H, H-3), 3.56 (s, 3H, OMe), 3.33 (ddd, 1H, H-5), 2.52 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 160.0, 137.9, 129.9 (each s, each aromatic C), 128.4, 127.8, 127.8, 113.5 (each d, each aromatic CH), 101.5, 101.4, 78.3, 76.7 (each d), 72.5 (t), 69.8 (d), 68.5 (t), 66.8 (d), 57.2, 55.2 (each q, each OCH_3); IR (KBr): 3429, 1637, 1517, 1250, 1090, 998 cm^{-1}; ES-HRMS: Found 425.1589, required 425.1576 $[M+Na]^+$.

4.1.7. Methyl 2-*O*-triisopropylsilyl-3-*O*-benzyl-4,6-*O*-(4-methoxybenzylidene)-β-D-mannopyranoside (22). Mannose derivative **8** (2.9 g, 7.2 mmol) and 2,6-lutidine (5.1 mL, 43.3 mmol) were dissolved in CH_2Cl_2 (35 mL) and cooled to 0°C. Triisopropylsilyl triflate (7.7 mL, 28.8 mmol) was added slowly and the solution was allowed to warm to room temperature and stirred for 12 h. The solution was washed with NH_4Cl (aq., 200 mL), water (200 mL) and concentrated. An analytical sample of **22** was obtained from chromatography of a small portion of the residue; the remainder of the material was used in the next reaction without further purification; $[\alpha]_D=-60.7$ (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–6.88 (overlapping signals, 9H, aromatic H), 5.56 (s, 1H), 4.75 (AB d, 2H, J=12.5 Hz, OCH_2Ph), 4.29 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=10.5 Hz, H-6a), 4.26 (overlapping signals, 2H, H-1,2), 4.12 (apt t, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 3.83 (apt t, 1H, $J_{5,6a}$=10.5 Hz, H-6b), 3.81 (s, 3H, OMe), 3.50 (dd, 1H, $J_{2,3}$=2.5 Hz, H-3), 3.45 (s, 3H, OMe), 3.29 (apt dt, 1H, H-5), 1.54–1.05 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 160.2, 138.9, 130.6 (each s, each aromatic C), 128.4, 128.0, 127.6, 113.5 (each d, each aromatic CH), 102.9, 101.7, 79.3, 78.3 (each d), 72.6 (t), 72.1 (d), 69.2 (t), 67.8 (d), 56.6, 55.5 (each q, each OCH_3), 29.9, 18.5, 18.4, 18.4, 13.2 (TIPS); IR (KBr): 2937, 2864, 1615, 1516, 1464, 1382, 1249, 1096, 1027 cm^{-1}; ES-HRMS: Found 581.2924, required 581.2911 $[M+Na]^+$.

4.1.8. Methyl-2-*O*-triisopropylsilyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-β-D-mannopyranoside (23). To a solution of **22** (7.21 mmol) in CH_2Cl_2 (200 mL) at 0°C was added DIBAL-H (36.1 mL of a 1.0 M solution in toluene, 36.1 mmol) dropwise over 30 min. The solution was allowed to warm to room temperature and was then washed with HCl (0.1 M, 200 mL), aq. $NaHCO_3$ (200 mL) and brine (200 mL). The organic phase was dried over $MgSO_4$, concentrated and purified to give **23** (3.6 g, 88.6% for 2 steps); $[\alpha]_D=-50.1$ (*c* 1.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–6.81 (overlapping signals, 9H, aromatic H), 4.69 (AB d, 2H, J=11.5 Hz, OCH_2Ph), 4.68 (AB d, 2H, J=10.5 Hz, OCH_2Ar), 4.24 (overlapping signals, 2H, H-1,2), 3.95 (apt t, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 3.83 (dd, 1H, $J_{5,6a}$=3.0 Hz, $J_{6a,6b}$=11.5 Hz, H-6a), 3.79 (s, 3H, PhOCH_3), 3.69 (dd, 1H, $J_{5,6b}$=4.5 Hz, H-6b), 3.43 (overlapping signals, 4H, H-3, OCH_3), 3.26 (d apt t, 1H, H-5), 1.26–0.69 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 159.3, 138.4, 130.5 (each s, each aromatic C), 129.9, 128.2, 127.6, 127.5, 113.8 (each d, each aromatic CH), 100.7 (d, C-1), 82.8 and 82.7, 75.4 (each d), 74.8 (t), 74.0 and 73.9 (d), 71.8, 71.8 (t), 70.3, 70.1 (d), 62.4 (t), 56.3 and 56.1, 55.3 (each q, each OCH_3), 21.0, 18.9, 18.2, 17.9, 17.8, 17.6, 17.0, 14.4, 14.2, 13.4, 13.2, 12.9 (TIPS); IR (KBr): 3496, 2944, 2865, 1612, 1514, 1463, 1374, 1249, 1076, 1006, 883, 822, 731, 677 cm^{-1}; ES-HRMS: Found 583.3073, required 583.3067 $[M+Na]^+$.

4.1.9. Methyl 2-*O*-triisopropylsilyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-*O*-tosyl-β-D-mannopyranoside (24). To a solution of **23** (3.4 g, 6.1 mmol) in anhyd. pyridine (25 mL) at 0°C was added *p*-toluenesulfonyl chloride (2.3 g, 12.2 mmol). The solution was stirred for 12 h then concentrated and purified by chromatography to provide **24** as a white solid (2.6 g, 59.7%); $[\alpha]_D=-25.8$ (*c* 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–6.81 (overlapping signals, 13H, aromatic H), 4.65 (AB d, 2H, J=12.0 Hz, OCH_2Ph), 4.58 (AB d, 2H, J=10.5 Hz, OCH_2Ar), 4.21 (br d, 1H, $J_{2,3}$=2.0 Hz, H-2), 4.19 (dd, 1H, $J_{5,6a}$=2.0 Hz, $J_{6a,6b}$=10.5 Hz, H-6a), 4.13 (s, 1H, H-1), 4.09 (dd, 1H, $J_{5,6b}$=4.5 Hz, H-6b), 3.80 (s, 3H, PhOCH_3), 3.74 (apt t, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 3.39 (dd, 1H, H-3), 3.37 (ddd, 1H, H-5), 3.34 and 3.33 (s, 3H, OCH_3), 2.42 (s, 3H, SPhCH_3,), 1.42–0.61 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 159.4, 144.5, 138.2, 133.1 (each s, each aromatic C), 130.1 and 130.1, 130.0, 129.7, 128.3, 128.0, 127.6 (each d, each aromatic CH), 127.5 (s, aromatic C), 113.9 (d, aromatic CH), 101.3 and 101.3 (each d, C-1), 82.6, 82.5 (d), 74.5 and 74.5 (each t), 73.2 and 73.2 (each d), 71.7 and 71.7 (each t), 69.8 and 69.6 (each d), 69.3 and 69.3 (each t), 56.0 and 55.9, 55.3 (each q, each OCH_3), 21.6 (q, CCH_3), 18.9, 18.2, 18.2, 17.9, 17.8, 17.8, 17.7, 17.0, 14.4, 13.3, 13.2, 12.8 (TIPS); IR (thin film): 3423, 2936, 2865, 1613, 1515, 1455, 1365, 1255, 1176, 1097, 977, 637 cm^{-1}; ES-HRMS: Found 737.3166, required 737.3155 $[M+Na]^+$.

4.1.10. Methyl 2-*O*-triisopropylsilyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-deoxy-6-azido-β-D-mannopyranoside (25). The tosylate **24** (2.35 g, 3.7 mmol) was dissolved in DMF (50 mL) and sodium azide (2.14 g, 32.8 mmol) was added. The solution was heated at 100°C and stirred for 2 h, then cooled and diluted with EtOAc (100 mL). The organic phase was washed with water (100 mL) and dried over $MgSO_4$. The crude residue was then purified by chromatography to give the title compound as a yellow oil (1.5 g, 77.8%); $[\alpha]_D=-18.2$ (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–6.82 (overlapping signals, 9H, aromatic H), 4.67 (AB d, 2H, J=12.0 Hz, OCH_2Ph), 4.65 (AB d, 2H, J=11.0 Hz, OCH_2Ar), 4.27 and 4.17 (pair of d, 1H, $J_{1,2}$=3.0 Hz, H-2), 4.20 (d, 1H, H-1), 3.79–3.72 (overlapping signals, 4H, ArOCH_3, H-4), 3.44 and 3.43 (pair of s, 3H, OCH_3), 3.42–3.32 (overlapping signals, 2H, H-3,5), 3.37–3.22 (overlapping signals, 2H, H-6a,6b), 1.26–0.61 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 159.3, 138.2, 130.2 (each s, each aromatic C), 129.9 and 129.9, 128.2, 127.6, 127.5, 127.5, 113.9 (each d, each aromatic CH), 101.4 and 101.3 (d, C-1), 82.8 and 82.7, 75.3, 74.6, 74.5 and 74.4 (each d), 71.6 and 71.5 (t), 70.0 and 69.7 (d), 55.9 and 55.8 (q, OCH_3), 55.2 (q, $PhOCH_3$), 51.9 and 51.8 (t), 18.8, 18.2, 18.1, 17.8, 17.8, 17.7, 17.7, 16.9, 14.4, 13.3, 13.2, 12.8 (TIPS); IR (thin film): 2926, 2865, 2097, 1612, 1514, 1454, 1369, 1250, 1100, 1008 cm^{-1}; ES-HRMS: Found 608.3161, required 608.3132 $[M+Na]^+$.

4.1.11. Methyl 2-*O*-triisopropylsilyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-deoxy-6-benzyloxycarbonylamino-β-D-mannopyranoside (26). The azide (0.25 g, 0.43 mmol) **25** was dissolved in EtOH/EtOAc (5:3, 8 mL) and the Lindlar catalyst (0.05 g) was added. The suspension was stirred under hydrogen (1 atm) for 12 h, then filtered and concentrated. The resulting residue containing the amine was dissolved in THF/water (1:1, 10 mL) and the solution was cooled to 0°C. Benzyl chloroformate (0.24 mL, 1.7 mmol) was added and the solution was allowed to warm to room temperature and stirred for 12 h. It was then diluted with EtOAc (20 mL) and the organic phase washed

with water, dried over $MgSO_4$ and concentrated. Purification by chromatography gave **26** (0.065 g, 21.6%); $[\alpha]_D=-30.0$ (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–6.82 (overlapping signals, 14H, aromatic H), 5.11 (overlapping signals, 3H, NH, CH_2 (cbz)), 4.68 (AB d, 2H, J=11.5 Hz, OCH_2Ph), 4.60 (AB d, 2H, J=10.0 Hz, OCH_2Ar), 4.22 (pair of d, 1H, J=2.5 Hz, H-2), 4.17 (br d, 1H, $J_{1,2}$=2.5 Hz, H-1), 3.76 (overlapping signals, 4H, H-4, $ArOCH_3$), 3.85 (m, 1H, H-6a), 3.41 and 3.40 (pair of s, 3H, OCH_3), 3.40 (overlapping signals, 2H, H-3,6b), 3.45 (apt dt, 1H, $J_{5,6a}$=4.5 Hz, $J_{5,6b}$=4.5 Hz, $J_{4,5}$=9.5 Hz, H-5), 1.59–0.90 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 159.4, 156.5, 138.4, 136.8 (each s), 130.4, 128.5 and 128.3, 127.9, 127.6 and 127.5, 113.9 (each d, each aromatic CH), 101.5 (d, C-1), 82.8 and 82.6 (d), 74.9 (t), 73.9, 73.8 (each d), 71.7 (t), 70.1 and 69.9 (d), 66.6 (t), 56.3 and 56.2 (q, OCH_3), 55.3 (q), 41.5 (t, CH_2N), 19.0, 18.3, 17.9, 17.8, 17.8, 17.0, 14.4, 13.4, 13.2, 12.8 (TIPS); IR (thin film): 3435, 2939, 2865, 1724, 1612, 1514, 1454, 1371, 1250, 1099 cm^{-1}; ES-HRMS: Found 716.3608, required 716.3594 $[M+Na]^+$.

4.1.12. Methyl 3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-deoxy-6-benzyloxycarbonylamino-β-D-mannopyranoside (11). Compound **26** (40 mg, 0.057 mmol) was dissolved in anhyd. THF (3 mL) and cooled to 0°C. Tetrabutylammonium fluoride (0.6 mL of a 1.0 M solution in THF, 0.6 mmol) was added and the solution was stirred for 30 min. The solvent was removed and the residue purified by chromatography to give **11** (0.025 g, 82%); $[\alpha]_D=-30.7$ (*c* 0.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–6.85 (overlapping signals, 14H, aromatic H), 5.16 (br d, 1H, J=5.5 Hz, NH), 5.11 (s, 2H, OCH_2, cbz group), 4.75 (AB d, 2H, J=10.0 Hz, OCH_2Ar), 4.61 (AB d, 2H, J=12.0 Hz, OCH_2Ph), 4.30 (br s, 1H, H-1), 4.07 (br d, 1H, J=2.5 Hz, H-2), 3.78 (s, 3H, $ArOCH_3$), 3.68 (apt t, 1H, $J_{3,4}$=9.0 Hz, $J_{4,5}$=9.0 Hz, H-4), 3.56 (overlapping signals, 3H, H-3,6a,6b), 3.51 (s, 3H, OCH_3), 3.29 (d apt t, 1H, $J_{5,6b}$=4.0 Hz, $J_{5,6b}$=4.0 Hz, $J_{4,5}$=9.0 Hz, H-5), 2.36 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 159.7, 156.6, 137.9, 136.8 (each s), 130.4, 128.8, 128.7, 128.3, 128.2, 128.1, 114.1 (each d, each aromatic CH), 101.0 (d, C-1), 81.7 (d), 75.2 (t), 74.5, 74.1 (each d), 71.8 (t), 68.4 (d), 67.0 (t), 57.4, 55.5 (each q, each OCH_3), 41.9 (t, CH_2N); IR (KBr): 3407, 2931, 1716, 1612, 1514, 1247, 1092 cm^{-1}; ES-HRMS: Found 560.2288, required 560.2260 $[M+Na]^+$.

4.1.13. Methyl-3-*O*-benzyl-6-deoxy-6-benzyloxy-carbonylamino-β-D-mannopyranoside (10). The mannose derivative **11** (0.037 g, 0.07 mmol) in CH_2Cl_2/H_2O (10:1, 1 mL) at 0°C was treated with DDQ (0.017 g, 075 mmol) and then allowed to warm to room temperature. After 2 h stirring it was washed with aq. $NaHCO_3$, dried over $MgSO_4$ and the solvent removed. Purification by chromatography gave **10** (0.025 g, 81.1%); $[\alpha]_D=-66.7$ (*c* 0.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–6.85 (overlapping signals, 10H, aromatic H), 5.34 (br s, 1H, NH), 5.10 (AB d, 2H, J=12.0 Hz, OCH_2Ph), 4.76 (s, 2H, CH_2, cbz), 4.31 (br s, 1H, $J_{1,2}$=1.0 Hz, H-1), 4.05 (dd, 1H, $J_{2,3}$=3.5 Hz, H-2), 3.79 (apt t, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=9.5 Hz, H-4), 3.76 (m, 1H, H-6a), 3.51 (s, 3H, OCH_3), 3.42 (overlapping signals, 2H, H-3,6b), 3.21 (d apt t, 1H, $J_{5,6a}$=3.5 Hz, $J_{5,6b}$=3.5 Hz, $J_{4,5}$=9.5 Hz, H-5), 2.36 (br s, 1H, OH), 1.71 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 157.8, 137.7, 136.1 (each s), 128.5, 128.5, 128.3, 128.1, 128.0, 127.9 (each d, each aromatic CH), 101.2 (d, C-1), 79.6, 75.0 (each d), 72.0 (t), 68.3 (d), 67.2 (t), 66.8 (d), 57.2 (q, OCH_3), 41.4 (t, CH_2N); IR (thin film): 3375, 2941, 1704, 1542, 1252, 1071 cm^{-1}; ES-HRMS: Found 440.1696, required 440.1685 $[M+Na]^+$.

4.1.14. Methyl 2-*O*-triisopropylsilyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-deoxy-6-acetylamino-β-D-mannopyranoside (27). The azide **25** (0.30 g, 0.51 mmol) was again dissolved in EtOH/EtOAc (5:3, 8 mL) and the Lindlar catalyst (0.05 g) was added. The suspension was stirred under hydrogen (1 atm) for 12 h, then filtered and concentrated. The resulting residue containing the amine was dissolved in acetic anhydride and pyridine (1:1, 3 mL) and stirred overnight. The solvent was removed and the residue filtered through a short column of silica to give **27** (0.27 g, 88%); $[\alpha]_D=-63.1$ (*c* 0.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–6.82 (overlapping signals, 9H, aromatic H), 5.77 (br t, 1H, J=7.0 Hz, NH), 4.70 (AB d, 2H, J=12.0 Hz, OCH_2Ph), 4.65 (AB d, 2H, J=10.0 Hz, OCH_2Ar), 4.23 and 4.13 (pair of d, 1H, $J_{1,2}$=2.5 Hz, H-2), 4.19 (d, 1H, H-1), 3.98–3.86 (m, 1H, H-6a), 3.81–3.71 (overlapping signals, 4H, H-4, $ArOCH_3$), 3.43 and 3.42 (pair of s, 3H, OCH_3), 3.43 (m, 1H, H-3), 3.35–3.24 (overlapping signals, 2H, H-5,6b), 1.94 and 1.93 (pair of s, 3H, $COCH_3$), 1.55–0.70 (overlapping signals, 21H, TIPS); ^{13}C NMR ($CDCl_3$): δ 170.2 (s, C=O), 159.6, 130.7, 130.6 (each s, each aromatic C), 128.5, 127.8, 127.8, 114.0 (each d, each aromatic CH), 100.8 (d, C-1), 83.0 and 82.8 (d), 75.1 (t), 74.0 and 73.8, 73.6 (each d), 72.1 (t), 70.5 and 70.2 (d), 56.5 and 56.4 (OCH_3), 55.5 ($PhOCH_3$), 39.7 and 39.6 (t, C-6), 23.4 (CH_3, NAc), 19.1, 18.5, 18.5, 18.2, 18.1, 17.3, 14.7, 13.6, 13.4, 13.0 (TIPS); IR (thin film): 2929, 2865, 1674, 1514, 1463, 1371, 1249, 1101 cm^{-1}; ES-HRMS: Found 624.3336, required 624.3333 $[M+Na]^+$.

4.1.15. Methyl-3-*O*-benzyl-4-*O*-(4-methoxybenzyl)-6-deoxy-6-acetylamino-β-D-mannopyranoside (12). Compound **27** (0.096 g, 0.16 mmol) was dissolved in anhyd. THF (3 mL) and cooled to 0°C. Tetrabutylammonium fluoride (75 mg, 0.3 mmol) was added and the solution was stirred for 30 min. The solvent was removed and the residue was purified by chromatography to give **12** (67 mg, 98%); $[\alpha]_D=-48.0$ (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–6.86 (overlapping signals, 9H, aromatic H), 5.87 (br s, 1H, NH), 4.73 (AB d, 2H, J=11.5 Hz, OCH_2Ph), 4.68 (AB d, 2H, J=10.0 Hz, OCH_2Ar), 4.32 (apt s, 1H, H-1), 4.08 (br d, 1H, $J_{2,3}$=3.0 Hz, H-2), 3.85 (ddd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,NH}$=7.5 Hz, $J_{6a,6b}$=14.0 Hz, H-6a), 3.80 (s, 3H, $ArOCH_3$), 3.67 (apt t, 1H, $J_{3,4}$=9.0 Hz, $J_{4,5}$=9.0 Hz, H-4), 3.60 (dd, 1H, H-3), 3.54 (s, 3H, OCH_3), 3.45 (ddd, 1H, $J_{5,6b}$=4.0 Hz, $J_{6b,NH}$=7.5 Hz, H-6b), 3.32 (m, 1H, H-5), 2.40 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 170.3 (s, C=O), 159.7, 137.9, 130.5 (each s, each aromatic C), 130.5, 128.8, 128.2, 128.2, 114.2 (each d, each aromatic CH), 101.2 (d, C-1), 81.7 (d), 75.3 (t), 74.5, 73.9 (each d), 71.9 (t), 69.4 (d), 57.4, 55.5 (each q, each OCH_3), 39.9 (t, CH_2N), 23.5 (s, $NHCOCH_3$); IR (thin film): 3459, 3297, 2920, 2856, 1642, 1556, 1515, 1454, 1371, 1251, 1171, 1067, 822, 789, 747, 699 cm^{-1}; ES-HRMS: Found 468.2007, required 468.1998 $[M+Na]^+$.

4.1.16. Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-azido-β-D-glucopyranoside. Methyl β-D-glucopyranoside (10.0 g, 49 mmol) was dissolved in pyridine (100 mL) and cooled (0°C). 4-Toluenesulphonyl chloride (16.0 g, 84.2 mmol) was added and the solution was allowed to warm to room temperature. After 24 h the reaction was concentrated. The crude material was dissolved in anhyd. DMF (175 mL) and sodium azide (31.9 g, 0.49 mol) was added. The reaction was stirred and heated (80°C) for 48 h to ensure completion, as both starting tosylate and product azide have the same mobility by TLC. The suspension was filtered to remove unreacted sodium azide and the filtrate was concentrated. To this was added acetic anhydride and pyridine (1:1, 100 mL) and the mixture was stirred for 15 h. The solution was concentrated and the residue was dissolved in CH_2Cl_2 (100 mL), washed carefully with aq. $NaHCO_3$ (100 mL), then water (100 mL) and dried over $MgSO_4$. Chromatography provided the title compound (10.7 g, 63.3% for 3 steps); $[\alpha]_D=-32.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.21 (apt t, 1H, $J_{2,3}$, $J_{3,4}$=9.5 Hz, H-3), 5.02–4.93 (overlapping signals, 2H, H-2,4), 4.46 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 3.70 (ddd, 1H, $J_{5,6a}$=2.5 Hz, $J_{5,6b}$=7.5 Hz, $J_{4,5}$=10.0 Hz, H-5), 3.53 (s, 3H, OCH_3), 3.42 (dd, 1H, $J_{6a,6b}$=13.5 Hz, H-6a), 3.20 (dd, 1H, H-6b), 2.05, 2.03 and 2.01 (each s, each 3H, each CH_3 (OAc)); ^{13}C NMR ($CDCl_3$): δ 170.3, 169.6, 169.4 (each s, each C=O), 101.5 (d, C-1), 73.7, 72.6, 71.2, 69.7 (each d), 57.0 (q, O*C*H_3), 51.2 (t, C-6), 20.7, 20.6, 20.6 (each q, each OAc); IR (KBr): 2944, 2101, 1767, 1375, 1223, 1048 cm^{-1}; CI-HRMS: Found 363.1515, required 363.1516 $[M+NH_4]^+$.

4.1.17. Methyl 6-deoxy-6-azido-β-D-glucopyranoside. Methyl 2,3,4-tri-*O*-acetyl-6-azido-β-D-glucopyranoside (10.35 g, 30 mmol) was dissolved in methanol (200 mL) and elemental sodium (0.1 g) was added. The solution was stirred for 16 h and then Amberlite IR-120 (plus) ion exchange resin was added. The solution was filtered, concentrated and passed through a bed of silica which gave the title compound (5.1 g, 78%); $[\alpha]_D=-23.5$ (*c* 0.02, EtOH); ^1H NMR (300 MHz, D_2O): δ 4.35 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 3.62–3.53 (overlapping signals, 2H, H-5,6a), 3.52 (s, 3H, OCH_3), 3.46 (m, 1H, H-6b), 3.43 (apt t, 1H, $J_{2,3}=J_{3,4}$=9.0 Hz, H-3), 3.36 (apt t, 1H, $J_{4,5}$=9.0 Hz, H-4), 3.22 (dd, 1H, H-2); ^{13}C NMR (D_2O): δ 103.5 (d, C-1), 75.8, 75.1, 73.3, 70.7 (each d), 57.5 (O*C*H_3), 51.2 (t, C-6); IR (KBr): 3395, 2124, 1643, 1097, 635 cm^{-1}; CI-HRMS: Found 237.1110, required 237.1199 $[M+NH_4]$.

4.1.18. Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-*tert*-butoxycarbonylamino-β-D-glucopyranoside. Methyl 6-deoxy-6-azido-β-D-glucopyranoside (5.15 g, 23.5 mmol) was dissolved in ethanol (40 mL) and shaken in a Parr hydrogenator in the presence of Pd/C (0.4 g) under an atm. of H_2. The reaction could not be brought to completion and so was filtered, concentrated and the unpurified material was used in the following step. Thus the residue was dissolved in anhyd. DMF and di-*tert*-butyl dicarbonate (5.65 g, 25.9 mmol) was added and the solution was stirred overnight at room temperature. For ease of purification the crude material was acetylated (Py./Ac_2O; 1:1, 100 mL) overnight and then the solvent was removed. Chromatography provided the title compound (3.3 g, 48% for 3 steps); $[\alpha]_D=-15.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.21 (apt t, 1H, $J_{2,3}$, $J_{3,4}$=9.5 Hz, H-3), 5.01–4.97 (overlapping signals, 2H, H-2,4), 4.87 (br s, 1H, NH), 4.43 (d, 1H, $J_{1,2}$=7.0 Hz, H-1), 3.57 (m, 1H, H-5), 3.52 (s, 3H, OCH_3), 3.44 (ddd, 1H, $J_{6a,NH}$=3.0 Hz, $J_{5,6a}$=6.5 Hz, $J_{6a,6b}$=11.5 Hz, H-6a), 3.38 (m, 1H, H-6b), 2.06 (s, 6H, OCH_3, OAc), 2.01 (s, 3H, OCH_3, OAc), 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$): δ 170.3, 169.6, 169.4 (each s, each C=O), 155.7 (s, Boc C=O), 101.6 (d, C-1), 79.7 (s, *C*CH_3), 72.9, 72.8, 71.3, 69.0 (each d), 60.0 (O*C*H_3), 40.6 (t, C-6), 28.3 (q, C(*C*H_3)$_3$), 20.7, 20.7, 20.6 (q, OAc); IR (KBr): 3421, 2980, 1757, 1716, 1521, 1373, 1280, 1234, 1060, 599 cm^{-1}; CI-HRMS: Found 420.1866, required 420.1870 $[M+H]^+$. Anal. Calcd for $C_{18}H_{29}NO_{10}$: C, 51.55; H, 6.97; N, 3.34. Found: C, 51.66; H, 7.03; N, 3.19.

4.1.19. Methyl 6-deoxy-6-*tert*-butoxycarbonylamino-β-D-glucopyranoside (13). Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-*tert*-butoxycarbonylamino-β-D-glucopyranoside (2.1 g, 5.0 mmol) was dissolved in methanol (50 mL) and elemental sodium (0.1 g) was added. The solution was stirred for 2 h and then amberlite IR-120 (plus) ion exchange resin was added. The solution was filtered, concentrated and filtered through silica to provide **13** (1.1 g, 71%); $[\alpha]_D=-38.8$ (*c* 1.0, MeOH); ^1H NMR (300 MHz, D_2O): δ 4.27 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 3.49 (overlapping signals, 4H), 3.43–3.33 (overlapping signals, 2H), 3.29–3.12 (overlapping signals, 3H), 1.38 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (Me_2SO-d_6): δ 156.5 (s, C=O), 104.4 (d, C-1), 78.3 (s, *C*(CH$_3$)$_3$), 77.0, 75.4, 74.1, 72.6 (each d), 56.5 (O*C*H_3), 42.5 (t, C-6), 29.0 (q, C(*C*H_3)$_3$); IR (KBr): 3390, 2975, 1695, 1521, 1449, 1367, 1260, 1188, 1065, 1004, 615 cm^{-1}; ES-LRMS: 316.2. $[M+Na]^+$. Anal. Calcd for $C_{12}H_{23}NO_7$: C, 49.15; H, 7.91; N, 4.78. Found: C, 48.83; H, 7.79; N, 4.63.

4.1.20. Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (28). The glucose derivative **18** (4.2 g, 11.3 mmol) in CH_2Cl_2/H_2O (50:1, 25 mL) was treated with trifluoroacetic acid (15 mL of 30% CH_2Cl_2 solution) and stirred for 0.5 h. Pyridine (50 mL) was then added, followed by acetic anhydride (50 mL) and the solution was allowed to stand overnight. It was then concentrated and purified by chromatography to provide **28** (4.4 g, 90%); $[\alpha]_D=-42.0$ (*c* 0.23, $CHCl_3$); The ^1H NMR data is identical with that previously reported;[25] ^{13}C NMR ($CDCl_3$): δ 170.8, 169.3, 169.3 (each s, each C=O), 137.8 (s, aromatic C), 128.4, 127.8, 127.8 (each d, each aromatic CH), 101.8 (d, C-1), 80.1 (d), 73.8 (t), 72.5, 72.1, 69.7 (each d), 62.3 (t), 56.7 (q, OCH_3), 20.9, 20.8 (each q, OAc); IR (KBr): 2966, 2884, 1746, 1453, 1376, 1219, 1036, 898, 700 cm^{-1}; ES-HRMS: Found 433.1489, required 433.1475 $[M+Na]^+$.

4.1.21. Methyl 3-*O*-benzyl-β-D-glucopyranoside (29). The acetylated derivative **28** (4.4 g, 10.2 mmol) was dissolved in methanol (30 mL) and elemental sodium (0.05 g) was added. The solution was stirred for 2 h and then amberlite IR-120 (plus) ion exchange resin was added. After 10 min. it was filtered, concentrated and eluted through a short column of silica to provide **29** (3.1 g, quantitative). The ^1H NMR data is identical with that previously reported;[25] ^{13}C NMR (D_2O): δ 137.7 (s, aromatic C), 129.0, 128.9, 128.6 (each d, each aromatic CH), 103.4

(d, C-1), 84.1, 76.1 (each d), 75.1 (t), 73.1, 69.6 (each d), 60.9 (t), 57.4 (q, OCH_3); IR (KBr): 3351, 2932, 1677, 1454, 1392, 1211, 1081, 1039, 891, 741, 699 cm^{-1}.

4.1.22. Methyl 3-*O*-benzyl-6-*O*-tosyl-β-D-gluco-pyranoside (30). A solution of **29** (3.1 g, 10.2 mmol) in anhyd. pyridine (50 mL) at 0°C was treated with *p*-toluenesulfonyl chloride (8.0 g, 42.4 mmol) then stirred for 1.5 h at room temperature. It was diluted with EtOAc (200 mL), washed several times with water, dried over $MgSO_4$ and the solvent was removed. A small amount was purified by chromatography to provide **30**; $[\alpha]_D=-8.5$ (*c* 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–6.92 (overlapping signals, 9H, aromatic H), 4.82 (AB d, 2H, J=11.5 Hz, OCH_2Ph), 4.38 (dd, 1H, $J_{5,6a}$=4.0 Hz, $J_{6a,6b}$=12.0 Hz, H-6a), 4.22 (br d, 1H, H-6b), 4.13 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 3.49 (s, 3H, OCH_3), 3.46–3.34 (overlapping signals, 4H, H-2,3,4,5), 2.03 (s, 3H, $SC_6H_4CH_3$,); IR (thin film): 3473, 2922, 2848, 1453, 1259, 1084, 1044, 810, 739 cm^{-1}.

4.1.23. Methyl 3-*O*-benzyl-6-deoxy-6-acetylamino-β-D-glucopyranoside (14). The tosylate **30** was dissolved in anhyd. DMF (50 mL) and sodium azide (25.4 g, 61.4 mmol) was added. The reaction was stirred and heated (80°C) for 16 h. The suspension was allowed to cool to room temperature and was filtered to remove unreacted sodium azide. The crude azide **31** was concentrated, redissolved in Et_2O (70 mL) and treated with triphenylphosphine (3.0 g, 11.5 mmol). The solution was stirred and heated at reflux for 16 h, water (25 mL) was then added. After 1 h the two phase mixture was cooled and concentrated. The crude amine **32** was acetylated (Py./Ac_2O; 1:1, 90 mL) and solvents were then removed in vacuo. Chromatography provided methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-6-deoxy-6-acetylamino-β-D-glucopyranoside (1.1 g, 25% for 4 steps); $[\alpha]_D=-124.0$ (*c* 0.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.21 (overlapping signals, 5H, aromatic H), 6.00 (br s, 1H, N*H*), 5.00 (dd, 1H, $J_{1,2}$=8.0 Hz, $J_{2,3}$=8.5 Hz, H-2), 4.95 (apt t, 1H, $J_{3,4}$, $J_{4,5}$=9.5 Hz, H-4), 4.59 (s, 2H, OCH_2Ph), 4.33 (d, 1H, H-1), 3.67 (dd, 1H, H-3), 3.64 (ddd, 1H, $J_{5,6a}$=3.0 Hz, $J_{6a,NH}$=6.0 Hz, $J_{6a,6b}$=14.0 Hz, H-6a), 3.53 (ddd, 1H, H-5), 3.48 (s, 3H, OCH_3), 3.26 (apt dt, 1H, $J_{6b,NH}$=6.0 Hz, $J_{5,6b}$=6.0 Hz, H-6b), 2.01, 2.00, 1.98 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$): δ 170.6, 170.0, 169.6 (each s, each C=O), 138.0 (s, aromatic C), 128.7, 128.1, 128.0 (each d, each aromatic CH), 102.1 (d, C-1), 80.2 (d), 74.3 (t, OCH_2Ph), 72.8, 70.8 (each d), 57.0 (q, OCH_3), 39.7 (t, C-6), 23.4, 21.1, 21.1 (each s, each Ac); IR (KBr): 3476, 2873, 1746, 1451, 1228, 1092, 741 cm^{-1}; CI-HRMS: Found 410.1811, required 410.1815 $[M+H]^+$.

Methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-6-deoxy-6-acetylamino-β-D-glucopyranoside (1.0 g, 2.4 mmol) was dissolved in methanol (20 mL) and elemental sodium (0.05 g) was added. The solution was stirred for 16 h and then amberlite IR-120 (plus) ion exchange resin was added. After 10 min. the solution was filtered, the solvent was removed and the residue eluted through a short column of silica to give **14** (0.78 g, quantitative); $[\alpha]_D=-88.0$ (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.26 (overlapping signals, 5H, aromatic H), 5.95 (br s, 1H, N*H*), 4.92 (AB d, 2H, J=11.5 Hz, OCH_2Ph), 4.28 (d, 1H, J=3.5 Hz, H-3), 4.23 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 4.09 (ddd, 1H, $J_{5,6a}$=2.5 Hz, $J_{6a,NH}$=9.0 Hz, $J_{6a,6b}$=15.0 Hz, H-6a), 3.56 (s, 3H, OCH_3), 3.48–3.35 (overlapping signals, 2H, H-2,4), 3.27 (apt t, 1H, H-5), 3.15 (ddd, 1H, J=2.5 Hz, J=5.0 Hz, H-6b), 2.36 (d, 1H, J=1.5 Hz, *OH*), 2.06 (s, 3H, NHAc); ^{13}C NMR ($CDCl_3$/Me_2SO-d_6; 10:1): δ 172.4 (s, C=O), 139.1 (s, aromatic C), 128.2, 127.9, 127.4 (each d, each aromatic CH), 104.4 (d, C-1), 83.4, 75.0 (each d), 74.7 (t, OCH_2Ph), 73.7, 70.7 (each d), 57.1 (q, OCH_3), 40.0 (t, C-6), 22.7 (s, NHAc); IR (KBr): 3480, 3303, 2911, 1638, 1561, 1379, 1093, 1041, 734 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_1O_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.81; H, 7.14; N, 4.26; ES-HRMS: Found 326.1616, required 326.1604 $[M+Na]^+$.

4.1.24. Phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (34); phenyl 3-*O*-pivalyl-4,6-*O*-benzylidene-β-D-glucopyranoside (9) and phenyl 3,6-di-*O*-pivalyl-β-D-glucopyranoside (15). A solution of **33** (10 g, 39 mmol), camphorsulphonic acid (50 mg) and benzaldehyde dimethylacetal (11.8 mL, 78.8 mmol) in MeCN (300 mL) was stirred for 12 h at room temperature. Triethylamine (5 mL) was added and the solution was allowed to stir for a further 1 h. The product **34** was then filtered off, washed with petroleum ether and was dried under diminished presssure (11.8 g, 88%); mp 163–165°C; $[\alpha]_D=-51.5$ (*c* 2.0, acetone) (lit.:[18] mp 179–181°C (EtOH); $[\alpha]_D=-66.5$ (*c* 2.0, acetone)); ^1H NMR (270 MHz, $CDCl_3$): δ 7.52–7.04 (overlapping signals, 10H, aromatic H), 5.54 (s, 1H, C*H*Ph), 5.04 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 4.39 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=10.5 Hz, H-6), 3.90 (apt t, 1H, $J_{2,3}$=9.0 Hz, $J_{3,4}$=9.0 Hz, H-3), 3.84–3.77 (overlapping signals, 2H, H-2, H-6), 3.63 (apt t, 1H, $J_{4,5}$=9.0 Hz, H-4), 3.57 (m, 1H, H-5), 2.81 (br s, 1H, OH), 2.70 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 156.7, 137.2 (each s, each aromatic C), 129.7, 129.4, 128.4, 126.3, 123.3, 116.8 (each d, each aromatic CH), 102.0, 101.1, 80.3, 74.3, 73.2 (each d), 68.6 (t, C-6), 66.6 (d); IR (KBr): 3584, 3371, 2925, 2885, 1634, 1592, 1497, 1386, 1228, 1082, 1031, 751, 698 cm^{-1}; ES-HRMS: Found 345.1338, required 345.1338 $[M+H]^+$.

To a cooled (0°C) mixture of **33** and **34** (4:9, 5.4 g), obtained from an acetalation reaction that had not gone to completion, in anhyd. pyridine (33 mL) was added trimethylacetyl chloride (5.5 mL). The solution was allowed to warm to room temperature and was stirred for a further 4 h. It was then diluted with EtOAc (100 mL) and the organic layer washed with HCl (0.1 M, 300 mL), aq. $NaHCO_3$ (100 mL) and brine (100 mL). It was dried over $MgSO_4$ and the solvent was removed. The title compounds were isolated after chromatography.

Analytical data for **9**; mp 144–145°C; $[\alpha]_D=-45.4$ (*c* 0.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.46–7.00 (overlapping signals, 10H, aromatic H), 5.54 (s, 1H, C*H*Ph), 5.26 (apt t, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, H-3), 5.10 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 4.38 (dd, 1H, $J_{5,6a}$=5.0 Hz, $J_{6a,6b}$=10.5 Hz, H-6a), 3.88 (br apt t, 1H, H-2), 3.80 (apt t, 1H, $J_{5,6b}$=10.5 Hz, H-6b), 3.77 (apt t, 1H, $J_{4,5}$=9.5 Hz, H-4), 3.63 (m, 1H, H-5), 1.25 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 178.9 (s, C=O), 156.9, 136.9 (each s, each aromatic C), 129.6, 128.9, 128.1, 125.9, 123.2, 116.9 (each d, each aromatic CH), 101.5 (d, C-1), 101.1 (d, *C*HPh), 78.2 (d, C-4), 73.7 (d, C-3), 73.3 (d, C-2), 68.5 (t, C-6), 66.3 (d,

C-5), 38.9 (s, $C(CH_3)_3$), 27.0 (q, CH_3); IR (KBr): 2963, 1719, 1481, 1229, 1078, 1038, 698 cm^{-1}; ES-LRMS: 451.2 $[M+Na]^+$. Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 66.96; H, 6.65.

Analytical data for **15**; mp 177–178°C; $[\alpha]_D=-21.0$ (*c* 5.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.27–7.02 (overlapping signals, 5H, aromatic H), 5.00 (apt t, 1H, $J_{2,3}=J_{3,4}=9.0$ Hz, H-3), 4.95 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.49 (dd, 1H, $J_{5,6a}=2.5$ Hz, $J_{6a,6b}=12.0$ Hz, H-6a), 4.22 (dd, 1H, $J_{5,6b}=7.5$ Hz, H-6b), 3.75 (overlapping signals, 2H, H-2,4), 3.53 (m, 1H, H-5), 3.25 (d, 1H, *J*=6.0 Hz, OH), 2.80 (br s, 1H, OH), 1.26 and 1.21 (each s, each 9H, each $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 180.2, 178.9 (each s, each C═O), 160.0 (s, aromatic C), 129.5, 123.0, 116.8 (each d, each aromatic CH), 100.7 (d, C-1), 77.5, 74.4, 72.0, 69.7 (each d), 63.8 (t, C-6), 39.1, 38.8 (each s, $C(CH_3)_3$), 27.1, 27.1 (q, CH_3); IR (KBr): 3568, 2970, 1726, 1491, 1289, 1166 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_8$: C, 62.25; H, 7.60. Found: C, 61.71; H, 7.49.

4.1.25. Phenyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-azido-β-D-glucopyranoside (35). Compound **33** (10.0 g, 39 mmol) was dissolved in pyridine (65 mL) and cooled (0°C). 4-Toluenesulfonyl chloride (12.6 g, 56.5 mmol) was added and the solution was allowed to warm to room temperature. After 16 h the reaction, though not complete, was concentrated. The crude material was dissolved in anhyd DMF (175 mL) and sodium azide (25.4 g, 0.39 mol) was added. The reaction was stirred and heated (80°C) for 16 h. The suspension was allowed to cool to room temperature and acetic anhydride and pyridine (1:1, 100 mL) were added. This was stirred for 15 h, diluted with CH_2Cl_2 (100 mL), washed carefully with aq. $NaHCO_3$ (3×100 mL), then aq. $CuSO_4$ (3×100 mL) and finally water (100 mL). The organic phase was dried over $MgSO_4$, the solvent was removed and the residue was purified by chromatography to yield the title compound (5.36 g, 34% for 3 steps); $[\alpha]_D=-68.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.00 (overlapping signals, 5H, aromatic H), 5.29–5.11 (overlapping signals, 2H, H-2,3), 5.13–5.04 (overlapping signals, 2H, H-1,4), 3.78 (ddd, 1H, $J_{4,5}=10.0$ Hz, $J_{5,6a}=3.0$ Hz, $J_{5,6b}=7.0$ Hz, H-5), 3.43 (dd, 1H, $J_{6a,6b}=13.0$ Hz, H-6a), 3.32 (dd, 1H, H-6b), 2.07, 2.05, 2.03 (each s, each 3H, CH_3 (Ac)); ^{13}C NMR ($CDCl_3$): δ 170.3, 169.5, 169.3 (each s, each C═O), 156.7 (s, aromatic C), 129.7, 123.6, 117.2 (each d, each aromatic CH), 99.3 (d, C-1), 73.5, 72.5, 71.1, 69.4 (each d), 51.2 (t, C-6), 20.6 (s, Ac); IR (KBr): 2094, 1758, 1493, 1375, 1217, 1050 cm^{-1}; ES-HRMS: Found 430.1125, required 430.1126 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{21}N_3O_8$: C, 53.07; H, 5.20; N,10.32. Found: C, 53.14; H, 5.11; N,9.77.

4.1.26. Phenyl 6-deoxy-6-acetylamino-β-D-glucopyranoside (16). Azide **35** (4.64 g, 11.4 mmol) was dissolved in Et_2O (40 mL) and triphenylphosphine (3.4 g, 13.0 mmol) was added. The solution was stirred and heated at reflux for 16 h, then water (50 mL) was added. After 1.5 h the biphasic mixture was cooled and concentrated. The crude mixture contained a number of products that were thought to result from acetate migration onto the newly formed amine. To confirm this a small amount (0.5 g crude) was acetylated (Py./Ac_2O; 1:1, 6 mL). TLC revealed the presence of just one compound, namely phenyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-acetylamino-β-D-glucopyranoside, which was isolated by chromatography; $[\alpha]_D=-32.0$ (*c* 0.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.08 (overlapping signals, 5H, aromatic H), 6.97 (br s, 1H, N*H*), 5.33–5.24 (overlapping signals, 2H, H-2,3), 5.13 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 5.03 (apt t, 1H, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4), 3.80 (ddd, 1H, $J_{5,6a}=2.5$ Hz, $J_{5,6b}=6.0$ Hz, H-5), 3.62 (ddd, 1H, $J_{6a,NH}=5.5$ Hz, $J_{6a,6b}=14.0$ Hz, H-6a), 3.45 (d apt t, 1H, $J_{6a,NH}=6.0$ Hz, H-6b), 2.09, 2.07, 2.04, 1.98 (each s, each 3H, each OAc); IR (KBr): 1746, 1656, 1550, 1437, 1374, 1224, 1234, 1080, 787 cm^{-1}; CI-HRMS: Found 424.1602, required 424.1608 $[M+H^+]$.

Some of of the mixture (7.1 mmol) was dissolved in MeOH and elemental sodium (0.1 g) was added. After 16 h amberlite IR-120 (plus) ion exchange resin was added and the solution was stirred for 10 min. It was then filtered and the solvent was removed. Recrystallisation from H_2O/MeOH provided the title compound **16** (1.5 g, 71%); $[\alpha]_D=-63.5$ (*c* 1.0, H_2O); ^1H NMR (300 MHz, D_2O): δ 7.36–7.00 (overlapping signals, 5H, aromatic H), 5.01 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 3.59–3.46 (overlapping signals, 4H, H-2,5,6a,6b), 3.35–3.27 (overlapping signals, 2H, H-3,4), 1.89 (s, 3H, CH_3); ^{13}C NMR (Me_2SO-d_6): δ 174.0 (s, C═O), 161.4 (s, aromatic C), 133.4, 125.8, 120.1, (each d, each aromatic CH), 104.4 (d, C-1), 80.1, 78.3, 77.3, 75.4 (each d), 42.7 (t), 26.5 (q, CH_3); IR (KBr): 3342, 2903, 1649, 1566, 1231, 1062, 692 cm^{-1}; ES-LRMS: Found 320.1 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{19}N_1O_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.51; H, 6.38; N, 4.52.

4.1.27. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside. To a stirred solution of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (1.55 g, 3.57 mmol) and 2,6-lutidine (3.68 mL, 31.2 mmol) in anhyd. CH_2Cl_2 (40 mL) at 0°C was added *tert*-butyldimethylsilyl triflate (3.68 mL, 16.0 mmol). The solution was allowed to warm to room temperature and the reaction was complete after 10 min. The solvent was removed and a small amount purified by chromatography to obtain an analytical sample; $[\alpha]_D=-59.2$ (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–6.97 (overlapping signals, 15H, aromatic H), 5.54 (s, 1H, CHC_6H_4), 5.04 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.84 (AB d, 2H, *J*=11.0 Hz, OCH_2Ph), 4.35 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=10.5$ Hz, H-6a), 3.85–3.67 (overlapping signals, 4H, H-2,3,4,6b), 3.56 (apt dt, 1H, $J_{4,5}=9.5$ Hz, $J_{5,6b}=9.5$ Hz, H-5), 0.85 (s, 9H, $C(CH_3)_3$), 0.11 and 0.10 (each s, each 3H, each $SiCH_3$); ^{13}C NMR ($CDCl_3$): δ 156.8, 138.4, 137.2 (each s, each aromatic C), 129.4, 128.9, 128.2, 128.1, 128.0, 127.5, 126.0, 122.5, 116.3 (each d, each aromatic CH), 101.2, 101.1, 81.8, 81.7 (each d), 75.0 (t), 64.7 (d), 70.8 (t), 66.1 (d), 25.8 (q, $C(CH_3)_3$), 18.1 (s, $C(CH_3)_3$), -4.3, -4.4 (each q, each $SiCH_3$); IR (KBr): 2927, 1598, 1494, 1235, 1089, 1030, 837, 750 cm^{-1}. CI-HRMS: Found 549.2675, required 549.2673 $[M+H]^+$.

4.1.28. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside, prepared as described above (50 mg, 0.9 mmol) was dissolved in a wet 30% TFA/CH_2Cl_2

solution (1 mL) and stirred for 30 min until the reaction was complete. Pyridine (2 mL) was added, followed by acetic anhydride (2 mL). After 16 h the solution was concentrated and chromatography gave the title compound (24 mg, 48% for two steps); $[\alpha]_D=-76.9$ (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–6.98 (overlapping signals, 10H, aromatic H), 5.09 (apt t, 1H, $J_{3,4}=9.5$ Hz, $J_{4,5}=9.5$ Hz, H-4), 4.92 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.75 (AB d, 2H, $J=11.5$ Hz, OCH_2Ph), 4.22 (dd, 1H, $J_{5,6a}=5.0$ Hz, $J_{6a,6b}=12.5$ Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}=2.5$ Hz, H-6b), 3.88 (dd, 1H, $J_{2,3}=9.0$ Hz, H-2), 3.66 (ddd, 1H, H-5), 3.62 (apt t, 1H, H-3), 2.05 and 1.89 (each s, each OAc), 0.89 (s, 9H, C(CH_3)$_3$), 0.17 and 0.13 (each s, each 3H, each SiCH_3); ^{13}C NMR ($CDCl_3$): δ 170.9, 169.8 (each s, each C=O), 156.9, 138.2 (each s, each aromatic C), 129.4, 128.4, 127.7, 127.6, 122.6, 116.4 (each d, each aromatic CH), 100.6 (d, C-1), 88.4 (d), 75.8 (t, *C*H$_2$Ph), 74.6, 72.1, 70.2 (each d), 62.6 (t, C-6), 25.9 (q, C(*C*H$_3$)$_3$), 20.7 (q, COCH$_3$), 18.1 (s, *C*(CH$_3$)$_3$), -4.0, -4.3 (each q, each Si*C*H$_3$); IR (KBr): 3435, 2929, 1746, 1590, 1495, 1358, 1223, 1050, 838, 783 cm^{-1}. CI-HRMS: Found 562.2840, required 562.2836 $[M+NH_4]^+$.

The reaction was carried out on a larger scale from unpurified phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (1.9 g, 3.5 mmol) and required 30 mL of the TFA solution. After 5 h the reaction was still not complete, and the formation of phenyl 3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside was observed (TLC analysis). The crude material was acetylated as before (50 mL pyridine, followed by 50 mL of acetic anhydride). Chromatography of the residue gave the title compound (0.8 g, 1.47 mmol, 42%) and phenyl 3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside.

Analytical data for phenyl 3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44–6.96 (overlapping signals, 10H, aromatic H), 5.08 (apt t, 1H, $J_{3,4}=9.5$ Hz, $J_{4,5}=9.5$ Hz, H-4), 4.92 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.80 (AB d, 2H, $J=11.5$ Hz, OCH_2Ph), 4.25 (dd, 1H, $J_{5,6a}=6.0$ Hz, $J_{6a,6b}=12.0$ Hz, H-6a), 4.10 (dd, 1H, $J_{5,6a}=2.0$ Hz, H-6b), 3.89 (dd, 1H, $J_{2,3}=9.5$ Hz, H-2), 3.76 (m, 1H, H-5), 3.69 (apt t, 1H, H-3), 2.05, 1.99 (each s, each 3H, each OAc); ^{13}C NMR ($CDCl_3$): δ 171.0, 169.9 (each s, each C=O), 157.3, 138.4 (each s, each aromatic C), 129.8, 128.7, 128.1, 123.4, 117.2 (each d, each aromatic CH), 101.2 (d, C-1), 81.6 (d), 74.9 (t), 74.4, 72.5, 69.9 (each d), 72.7 (t), 21.0, 20.9 (each s, each OAc); IR (KBr): 3452, 2893, 1745, 1597, 1494, 1376, 1217, 1061, 752, 686 cm^{-1}.

4.1.29. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-6-*O*-tosyl-β-D-glucopyranoside. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside (0.8 g, 1.47 mmol) was dissolved in methanol (50 mL) and sodium (0.05 g) was added. The solution was stirred for 20 min and then Amberlite IR-120 (plus) ion exchange resin was added. After 5 min the solution was filtered and the solvent removed. The residue (0.04 g, 0.087 mmol) was dissolved in pyridine (0.5 mL) and cooled to 0°C. Initially tosyl chloride (0.0174 g, 0.091 mmol) was added and some product was formed after 20 min. (TLC analysis). The reaction was allowed to warm to room temperature and after 1 h more product had formed, however there was still substantial amounts of starting material. The solution was cooled and another 8 equiv. of tosyl chloride were added. The reaction was still not complete after a further 24 h. The mixture was then diluted with ethyl acetate (10 mL) and the excess tosyl chloride removed by several aqueous washes. Chromatography gave the title compound (0.035 g, 0.057 mmol, 65.5%); ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–6.92 (overlapping signals, 14H, aromatic H), 4.87 (AB d, 2H, $J=12.0$ Hz, OCH_2Ph), 4.85 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.31 (dd, 1H, $J_{5,6a}=2.0$ Hz, $J_{6a,6b}=11.0$ Hz, H-6a), 4.15 (dd, 1H, $J_{5,6b}=5.5$ Hz, H-6b), 3.72 (dd, 1H, $J_{2,3}=8.5$ Hz, H-2), 3.56 (ddd, 1H, $J_{4,5}=9.5$ Hz, H-5), 3.37 (dd, 1H, $J_{3,4}=8.5$ Hz, H-4), 3.39 (apt t, 1H, H-3), 2.36 (s, 3H, ArCH_3), 2.08 (br s, 1H, OH), 0.90 (s, 9H, C(CH_3)$_3$), 0.17 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 156.8, 144.7, 138.5, 132.6 (each s, each aromatic C), 129.6, 129.4, 128.8, 128.1, 128.0, 129.9, 116.6 (each d, each aromatic CH), 100.3 (d, C-1), 85.4 (d), 75.7 (t), 74.3, 73.4, 69.4 (each d), 68.6 (t), 25.9 (q, C(*C*H$_3$)$_3$), 18.1 (s, *C*(CH$_3$)$_3$), -4.0, -4.3 (each q, each Si*C*H$_3$); IR (KBr): 3470, 2927, 2856, 1598, 1495, 1359, 1231, 1176, 1082, 980, 836, 781 cm^{-1}.

The reaction of phenyl 2-*O*-tertbutyldimethylsilyl-3-*O*-benzyl-4,6-di-*O*-acetyl-β-D-glucopyranoside (0.65 g, 1.37 mmol) as described above (7 eq of tosyl chloride) gave complete conversion to the title compound which was used without further purification for the preparation of **36**.

4.1.30. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-6-deoxy-6-azido-β-D-glucopyranoside (36). Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-6-*O*-tosyl-β-D-glucopyranoside (0.066 g, 0.08 mmol) was dissolved in DMF (2 mL) and sodium azide (0.052 g, 0.8 mmol) was added. The suspension was stirred and heated at 90°C for 16 h, after which time the reaction was complete. The solution was diluted with ethyl acetate (10 mL) and the excess sodium azide removed with several aqueous washes (10 mL). Filtration through silica gave the azide **36** (0.035 g, 0.072 mmol, 90.2% for two steps); $[\alpha]_D=-128$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–6.99 (overlapping signals, 10H, aromatic H), 4.93 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.85 (AB d, 2H, $J=12.0$ Hz, OCH_2Ph), 3.81 (dd, 1H, $J_{2,3}=8.5$ Hz, H-2), 3.64–3.36 (overlapping signals, 5H, H-3,4,5,6a,6b), 1.92 (br s, 1H, OH), 0.92 (s, 9H, C(CH_3)$_3$), 0.21, 0.20 (each s, each 3H, Si(CH_3)); ^{13}C NMR ($CDCl_3$): δ 156.8, 138.5 (each s, each aromatic C), 129.5, 128.9, 128.2, 127.9, 122.5, 116.5 (each d, each aromatic CH), 100.6 (d, C-1), 85.7 (d), 75.7 (t, *C*H$_2$Ph), 74.8, 74.6, 70.5 (each d), 51.6 (t, C-6), 25.9 (q, C(*C*H$_3$)$_3$), 18.1 (s, *C*(CH$_3$)$_3$), -4.0, -4.3 (each q, each Si*C*H$_3$); IR (KBr): 2927, 2855, 2101, 1599, 1495, 1360, 1231, 1069, 852, 753, 695 cm^{-1}; CI-HRMS: Found 503.2686, required 503.2690 $[M+NH_4]^+$.

The reaction was repeated using 1.05 g of the tosylate (1.27 mmol) and this gave **36** which was purified by chromatography (0.45 g, 73%).

4.1.31. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4-*O*-ethyl-6-deoxy-6-azido-β-D-glucopyranoside. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-6-deoxy-6-azido-β-D-glucopyranoside **36** (0.43 g, 0.89 mmol) was dissolved in anhyd. THF (20 mL) and cooled to 0°C. Sodium hydride

(0.2 g, 8.9 mmol) was added and the suspension was stirred for 20 min. Ethyl iodide was added and the mixture was warmed to room temperature. After 3 h the reaction was quenched by careful addition of methanol. The solution was then diluted with ethyl acetate (100 mL) and washed with water (2×100 mL). Chromatography gave recovered starting material (0.078 g, 0.16 mmol, 18%) and also provided the title compound (0.375 g, 82%); $[\alpha]_D=-55.9$ (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–6.99 (overlapping signals, 10H, aromatic H), 4.90 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.88 (s, 2H, OCH_2Ph), 3.83–3.74 (overlapping signals, 2H), 3.62–3.48 (overlapping signals, 4H), 3.42 (apt t, 1H, $J=6.5$ Hz), 3.33 (apt t, 1H, $J=9.0$ Hz), 1.11 (t, 3H, $J=7.0$ Hz, OCH_2CH_3), 0.87 (s, 9H, $C(CH_3)_3$), 0.15, 0.09 (each s, each 3H, $Si(CH_3)$); ^{13}C NMR ($CDCl_3$): δ 159.6, 138.6 (each s, each aromatic C), 129.4, 128.2, 127.4, 127.2, 122.5, 116.5 (each d, each aromatic CH), 100.8 (d, C-1), 85.4, 79.0 (each d), 75.6 (t, CH_2Ph), 74.7, 74.6 (each d), 68.6, 51.5 (each t), 25.9 (q, $C(CH_3)_3$), 18.1 (s, $C(CH_3)_3$), 15.7 (q, CH_3 (OEt)), -4.0, -4.3 (each q, each $SiCH_3$); IR (KBr): 2928, 2856, 2100, 1599, 1495, 1360, 1283, 1231, 1160, 1092, 1066, 838, 779 cm^{-1}; CI-HRMS: Found 531.3003, required 531.3003 $[M+NH_4]^+$.

4.1.32. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4-*O*-ethyl-6-deoxy-6-acetylamino-β-D-glucopyranoside. Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4-*O*-ethyl-6-deoxy-6-azido-β-D-glucopyranoside (0.25 g, 0.48 mmol) was dissolved in EtOH and EtOAc (10:1, 20 mL) and the Lindlar catalyst (0.25 g) was added. This was stirred under a balloon of hydrogen for 30 min, then filtered and the solvent was removed. This gave the crude amine cleanly (0.23 g, 98%). Some of this material (0.52 g, 0.109 mmol) was acetylated with acetic anhydride (0.5 mL) and pyridine (0.5 mL). Chromatography gave the title compound (0.05 g, 86% for 2 steps); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–6.84 (overlapping signals, 10H, aromatic H), 5.67 (br t, 1H, $J=5.5$ Hz, NH), 4.82 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.78 (s, 2H, OCH_2Ph), 3.71–3.31 (overlapping signals, 7H), 3.13 (apt t, 1H, $J=9.0$ Hz), 1.84 (s, 3H, NAc), 1.05 (t, 3H, $J=7.0$ Hz, CH_2CH_3), 0.77 (s, 9H, $C(CH_3)_3$), 0.05, 0.00 (each s, each 3H, $Si(CH_3)$); ^{13}C NMR ($CDCl_3$): δ 169.8 (s, C=O), 156.8, 138.5 (each s, each aromatic C), 129.5, 128.2, 127.4, 127.3, 122.4, 115.9 (each d, each aromatic CH), 100.0 (d, C-1), 85.3, 79.5 (each d), 75.6 (t, CH_2Ph), 74.5, 73.6 (each d), 68.7, 40.0 (each t), 25.9 (q, $C(CH_3)_3$), 23.2 (q, NAc), 18.1 (s, $C(CH_3)_3$), 15.7 (q, CH_3), -4.1, -4.3 (each q, each $SiCH_3$); IR (KBr): 3295, 2948, 2856, 1655, 1599, 1562, 1495, 1360, 1232, 1163, 1081, 839, 760, 587 cm^{-1}; CI-HRMS: Found 530.2935, required 530.2938 $[M+H]^+$.

4.1.33. Phenyl 3-*O*-benzyl-4-*O*-ethyl-6-deoxy-6-acetylamino-β-D-glucopyranoside (37). Phenyl 2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-4-*O*-ethyl-6-deoxy-6-acetylamino-β-D-glucopyranoside (0.040 g, 0.079 mmol) was dissolved in anhyd. THF (2 mL) and the solution was cooled to 0°C. Tetrabutylammonium fluoride (0.42 mg, 0.17 mmol) was added and the solution was stirred for 30 min. The solvent was removed and the residue purified by chromatography to give **37** (0.032 g, 97%); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–6.98 (overlapping signals, 10H, aromatic H), 5.74 (br s, 1H, NH), 4.91 (d, 1H, $J_{1,2}=7.5$ Hz, H-1), 4.89 (s, 2H, OCH_2Ph), 3.86 (m, 1H), 3.76–3.64 (overlapping signals, 3H), 3.61–3.48 (overlapping signals, 3H, H-3,5,6b), 3.24 (apt t, 1H, $J_{3,4}=9.0$ Hz, $J_{5,4}=9.0$ Hz, H-4), 2.40 (br s, 1H, OH), 1.96 (s, 3H, NAc), 1.23 (m, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 170.0 (s, C=O), 156.9, 138.4 (each s, each aromatic C), 129.7, 128.6, 128.1, 128.0, 123.1, 116.6 (each d, each aromatic CH), 100.3 (d, C-1), 83.9, 78.9 (each d), 75.3 (t, CH_2Ph), 74.1, 73.9 (each d), 68.8, 40.0 (each t), 23.3 (q, CH_3 (NAc)), 15.8 (q, CH_3); IR (KBr): 3330, 2924, 2859, 1655, 1565, 1497, 1233, 1104, 1077, 766, 567 cm^{-1}; CI-HRMS: Found 416.2071, required 416.2073 $[M+H]^+$.

Acknowledgements

The authors thank George L. Trainor and Susan Erickson-Viitanen at Bristol Myers Squibb, Regine S. Bohacek and Novartis Pharmaceuticals for providing Growmol, C. Gregory Paris, Novartis Pharmaceuticals, for training in use of Growmol and Ralph Hirschmann for assistance in preparation of introductory material. P. M. and J. O'B. thank Enterprise Ireland for International Collaboration Travel Grants. P. M. thanks the Health Research Board (Irl.) and the Welcome Trust for an equipment grant, and Entreprise Ireland (SC/02/225) for funding.

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