A convenient synthesis of orthogonally protected 2-deoxystreptamine (2-DOS) as an aminocyclitol scaffold for the development of novel aminoglycoside antibiotic derivatives against bacterial resistance†

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The development of new aminoglycoside analogues to reduce the emergence of bacterial resistance has become a topic of high interest. We describe here a rapid and facile access to orthogonally protected 2-deoxystreptamine (2-DOS), a *meso*-diaminocyclitol known to be a pivotal component of most active aminoglycosides. Our synthetic approach started from highly protected methyl α-D-glucopyranoside which in turn was converted by a Ferrier rearrangement into an enantiopure polyfunctionalized cyclohexane ring. Finally, two different N-protected groups were successively introduced. The first one was inserted as an oximino benzylether followed by a diastereofacial hydride reduction, working with $Me_4NBH(OAc)_3$ only in TFA at low temperature rather than in AcOH as usual. The second group was introduced by displacement of a hydroxyl group through a Mitsunobu reaction using a DPPA–DIAD–Ph_3P system for azide transfer.

Introduction

Aminoglycosides constitute a large family of small molecules that display a powerful antibacterial drug activity by causing a miscoding in protein biosynthesis and consequently the death of a bacterial cell.[1] In this regard they are widely used as clinically important antibacterial agents. Indeed, their antibiotic activity takes place specifically in the aminoacyl tRNA decoding site (A-site) located in a well defined region of the 16S rRNA (ribosomal RNA) within the 30S subunit of the bacterial ribosome.[2] Thus, these aminoglycosides, connected to particular oligonucleotides of the rRNA, disturb the fidelity of mRNA translation, leading to a misreading of bacterial protein elongation.

Unfortunately, during the last few decades, more and more resistant strains develop[1b,d,3] enzymes that modify these natural aminoglycosides, which thus become ineffective in the treatment of various infections. Faced with this increasing emergence of bacterial resistance to multiple antibiotics, the access to novel active aminoglycoside antibiotic derivatives will therefore represent a major goal.[3d] To this end, a library of numerous analogues of antibiotics has been obtained, by chemical modifications, from their parent aminoglycosides (often neamine or paromanine subunits). The main drawbacks, limiting this option of structural modifications, lie in problems of regiospecificity of protection–deprotection (for further incorporation of various substitutes), multi-step reactions, low solubility, difficulties in purification and tedious NMR characterization.

Notably, a majority of aminoglycosides such as kanamycin, neomycin, tobramycin, paromomycin, amikacin, ribostamycin, gentamicin, apramycin... are based on a central diaminocyclitol core named 2-deoxystreptamine (2-DOS) that is *O*-substituted at the 4, 5 and/or 6-position by an additional carbohydrate unit (Fig. 1). This recurring presence of 2-DOS core scaffold suggests an important role for its recognition at the bacterial rRNA target.[1d,4] In this way, a highly functionalized 2-DOS becomes an interesting polyvalent entity with the advantage of more flexibility in the elaboration and development of a suitable range of modified antibiotics able to mimic the aminoglycosides' potency.[5]

Syntheses of minimally protected or naked 2-deoxystreptamine have been performed by degradations of natural antibiotic sources[6] requiring further desymmetrization of the 2-DOS *meso* compound.[1d,7] Alternatively, it is more convenient to build polyprotected 2-DOS by modifications and successive incorporation of different protecting groups starting from an existing carbohydrate derivative precursor,[8] or from a chiral pool like D-allylglycine.[9] However, the few given literature examples are often low-yielding, multi-step syntheses that require separation of diastereomers. For all these reasons, we chose to investigate an efficient and convenient orthogonally protected 2-DOS synthesis. We report herein two inexpensive approaches towards the synthesis of highly functionalized *meso* 2-deoxystreptamine (2-DOS) in 7 and 11 steps respectively.

Results and discussion

Our objective was to minimize the number of steps and to use procedures for which each protected intermediate would be readily obtained by simple crystallization in very good yields and on a large scale. The orthogonal protection should allow for the regioselective introduction of different substituents in order to give access to a range of new mimetic antibiotics. Thus the starting point was the readily available methyl α-D-glucopyranoside[10] which can be transformed to a pentahydroxylated cyclohexane (quercitol) by a Ferrier carbocyclization rearrangement.[11]

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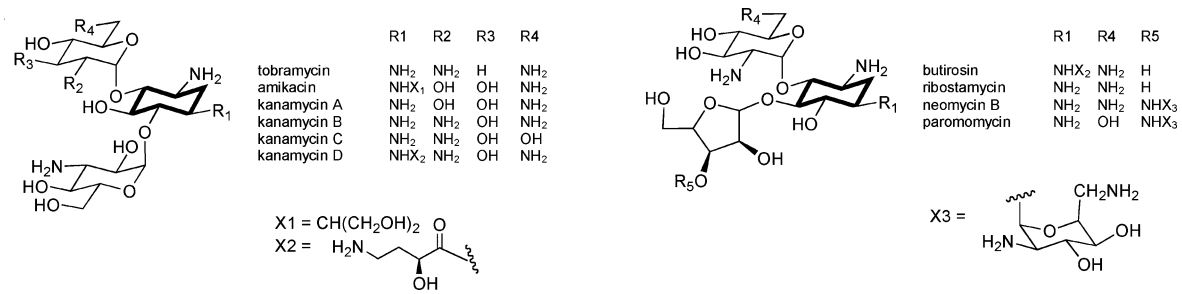
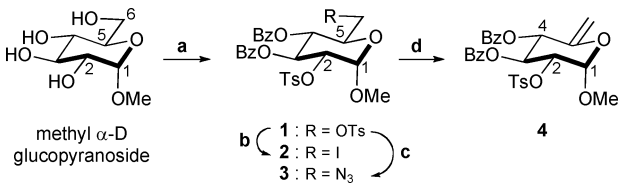


Fig. 1 Structures of selected common aminoglycoside antibiotics containing the *meso*-diaminocyclitol (2-DOS) unit.

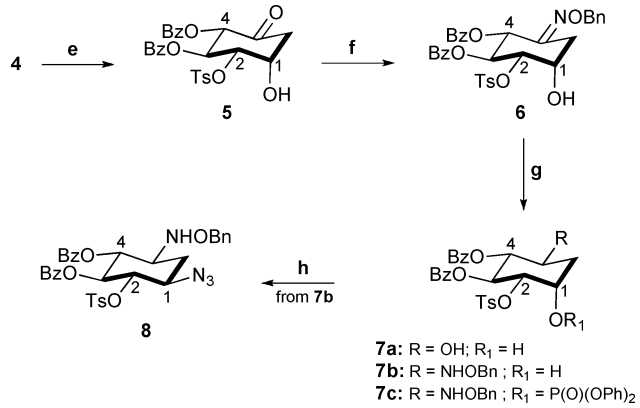
Our strategy began by the known one-step protection of methyl α-D-glucopyranoside to isolate compound **1** in 92% yield by simple crystallization in MeOH (Scheme 1).[12] As depicted in Scheme 1, the tosyl group on the C-6 primary alcohol was then easily substituted to give, in very good yield, either the iodide **2**[12a] (NaI, Ac_2O, 93%) or the azide **3** (NaN_3, dioxane, 95%) as crystalline products. Compound **3** is a useful precursor for the synthesis of the aminoglucosides kanamycin A or D bearing the 2-DOS unit, or for applications in click chemistry[13a] to link two carbohydrate moieties through a triazole ring as recently published.[13b–c] Dehydroiodination of **2** was cleanly performed (68% yield) in toluene with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[14] instead of silver fluoride as described earlier to give the expected enopyranoside **4**.[12a] Enone **4** was then subjected to the Ferrier carbocyclic ring-closure in the presence of $Hg(OAc)_2$ in a refluxing mixture of acetone–H_2O–AcOH to give **5**[12a,15] in 69% yield after recrystallization from CH_2Cl_2 (Scheme 2). This compound was isolated as a single epimeric β-hydroxy-cyclohexanone where the hydroxyl group has an axial orientation as shown by vicinal coupling ($J_{2,1} = 2.5$ Hz).



Scheme 1 *Reagents and conditions*: ref. 12*a* for (a) and (b), 92% and 93% respectively; (c) NaN_3, dioxane–H_2O, 110 °C, 48 h (95%); (d) from **2**: DBU, PhMe, 80 °C, 15 h (68%).

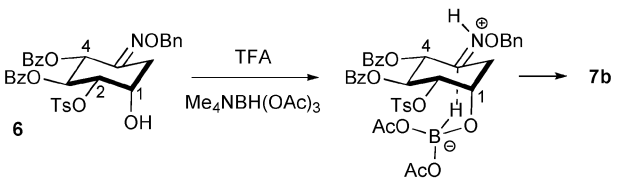
Now the first amino group was introduced at the carbonyl position through an oxime precursor using *O*-benzylhydroxylamine hydrochloride in EtOH–pyridine to afford the crystalline benzyloxime **6** in 93% yield without further purification (on the basis of NMR analysis). For the next step, the asymmetric reduction of this oximino ether has to be discussed.

Generally, the reduction of an imino (C=N) bond with borane or aluminium hydride reagents results in an isomeric mixture and/or the corresponding free amine after N–O bond cleavage.[8c,e,f,16] Literature precedents[17] show that tetramethylammonium triacetoxyborohydride (TABH)[18] can undergo a stereocontrolled reduction of acyclic β-hydroxy oximino benzyl ether to give *trans* 1,3-amino alcohols. More typically, TABH is used in the diastereoselective reduction of acyclic β-hydroxy ketones to provide *trans* 1,3-diols. The latter is proposed to involve the formation of a six-membered boron complex intermediate, prior to reduction.[18,19]



Scheme 2 *Reagents and conditions*: (e) ref. 12*a*, $Hg(OAc)_2$, acetone, H_2O, AcOH, 70 °C, 2.5 h (69%); (f) $BnONH_2$·HCl, EtOH, pyridine, RT, 6 h (93%); (g) **7a** from **5**: $Me_4NBH(OAc)_3$, AcOH, 0 °C, 1.5 h (80%); **7b** from **6**: $Me_4NBH(OAc)_3$, TFA, 0 °C, 2 h (93%); **7c** from **6**: DPPA, DBU, RT, 10 h (71%); (h) from **7b**: DPPA, Ph_3P, DIAD, RT, 7 h (65%).

In our case, the oximino benzyl ether function is located on a rigid cyclohexane unit. The axial β-hydroxyl group should play an essential role in the hydride reduction to participate in a neighboring group effect *via* coordination to the boron group of TABH, thereby allowing control of diastereofacial selectivity (see Scheme 3). With this in mind, we expected the asymmetric reduction of β-hydroxy oximinobenzyl ether **6** with this mild and selective reducing TABH agent to provide the optically active *trans* 1,3-benzyloxyamino alcohol **7b** (Scheme 3).



Scheme 3 Treatment with AcOH instead of TFA gave exclusively starting material **6** (see text).

Surprisingly, the typical treatment on **6** (TABH in MeCN–AcOH) failed and exhibited only starting material as summarized in Table 1 (entries 4, 5). However, applying identical conditions to the β-hydroxyketone **5** (entries 1–3) furnished the expected quercitol **7a**.[20] This quercitol, named (+)-viburnitol,[21] was rapidly formed and isolated in good yield (80%). We were able to assign

Table 1 Reduction conditions of ketone **5** or oximes **6** and **17** with TABH in the presence of AcOH or TFA[a]

Entry	Ketone and oxime	Acid (equiv.)	Time/h	Yield (%) of benzyloxyamine
1	**5**	AcOH (560)	0.5	84
2	**5**	AcOH (530)	1	80
3	**5**	AcOH (518)	0.5	65
4	**6**	AcOH (441)	6	0[b]
5	**6**	AcOH (774)	[c]	0[b]
6	**6**	TFA (473)	1.5	65
7	**6**	TFA (415)	1	66
8	**6**	TFA (152)	2	93
9	**6**	TFA (76)	30	89
10	**17**	TFA (151)	2.5	69

[a] All the experiments were performed with 10 to 11 equiv. of TABH ($Me_4NBH(OAc)_3$). For entries 1–5, standard conditions were used (TABH, MeCN, AcOH) and in entries 6–11, AcOH was replaced by TFA. [b] Exclusively starting material was observed. [c] Only starting material was present even after 5 h at room temperature and then 48 h at 55 °C.

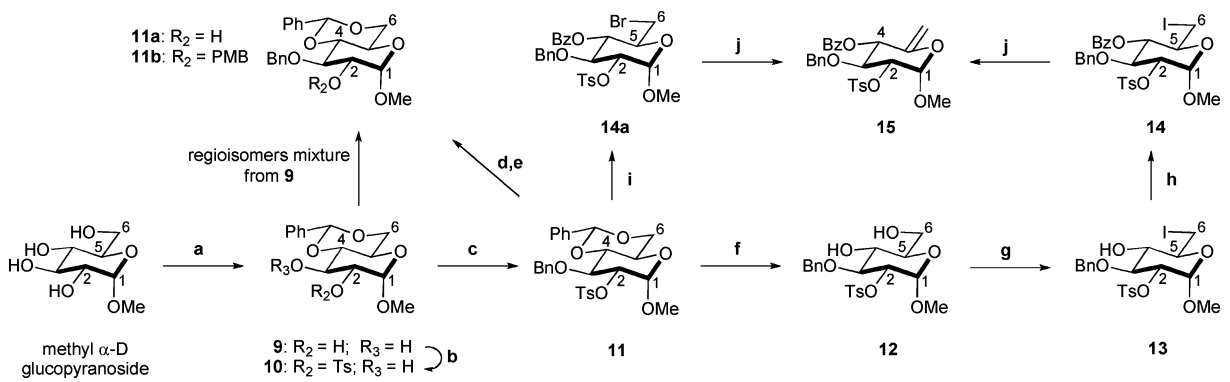
unambiguously its absolute configuration. The configuration of the newly generated hydroxyl group at C-5 was determined by NMR spectroscopy. The large coupling constants, $J_{4,5}$ (9.7 Hz) and $J_{5,6ax}$ (14.2 Hz) as well as $J_{5,6eq}$ (4.7 Hz), revealed that the new hydroxyl group in **7a** was oriented in an equatorial position.

Nevertheless, neither excess of AcOH nor increasing the time of reaction, even by heating for 48 h, produced any effect on the reduction of the oximinium intermediate (entries 4, 5 in Table 1). Gratifyingly, slightly modified conditions such as the use of the stronger acid TFA (trifluoroacetic acid) instead of AcOH, furnished cleanly the desired optically pure benzyloxyamino alcohol **7b** in 94% yield after only 2 h at low temperature and with at least 152 equivalents of TFA (entry 8). Moreover, no cleavage of the N–O bond and no dehydratation to enoxime were observed under these conditions. If less TFA was used (entry 9), more time was required for the reaction to reach completion.

Again, the stereochemistry of **7b** was fully characterized by NMR spectroscopic analysis that indicated that the amino group was only equatorial. The large coupling between H-4 and H-5 ($J_{4,5}$ = 10.0 Hz), as well as between H-6ax and H-5 ($J_{6ax,5}$ = 12.2 Hz), shows that all these protons have an axial position, while the relatively small coupling between H-6eq and H-5 ($J_{6eq,5}$ = 4.0 Hz) suggests that the amino group in **7b** adopts an equatorial orientation.

Finally, the next strategy was the use of diphenylphosphoryl azide (DPPA) as an azide transfer reagent to convert the axial hydroxyl group at C-1 directly into an equatorial azide functional group, which acts as an amine precursor. In this way, Mitsunobu type conditions were used for the incorporation of the azide, following the procedure described in the literature.[22] Thus, reaction of alcohol **7b** with triphenylphosphine (Ph_3P), diisopropyl azodicarboxylate (DIAD), and DPPA provided the azide **8** in good yield (65%) resulting in complete stereocontrol for the overall conversions. The stereochemistry of **8** was confirmed by ^{1}H NMR spectroscopy: $J_{6ax,1} = J_{6ax,5}$ 13.3 Hz and $J_{6eq,1} = J_{6eq,5}$ 4.4 Hz, as well as by NOESY analysis (see Experimental part). Attempts to apply a modification of this Mitsunobu azidation (DPPA and DBU) according to Thompson's procedure[23] was ineffective and yielded only the formation of the phosphate ester **7c** (71%).[24] This completes the synthesis of a 2-DOS derivative with two differentiated amine functionalities.

Alternatively, it was also interesting and attractive to envisage the synthesis of orthogonally protected 2-DOS starting from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **9** (Scheme 4). This new approach has the advantage of locking simultaneously and selectively the primary and the secondary alcohols at C-6 and C-4 to avoid, in this way, the double benzoyl protection at C-3 and C-4 of the above method.



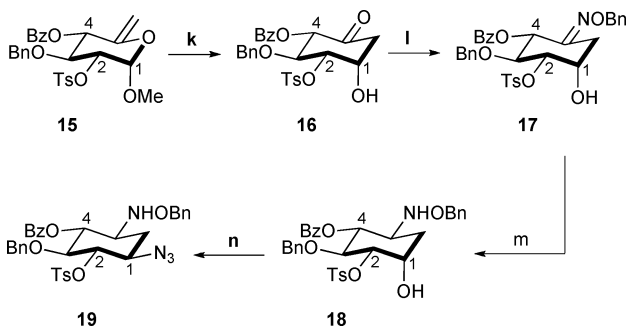
Scheme 4 *Reagents and conditions*: (a) $PhCH(OMe)_2$, *p*TsOH, DMF, 84 °C, 1.5 h (73%); (b) *p*TsCl, Bu_2SnO (82%) or Ts·Im, MeONa (56%); (c) BaO, $Ba(OH)_2{\cdot}8H_2O$, BnBr, DMF, 0 °C to RT, 8 h (87%); (d) DMSO, $NaBH_4$, 0 °C then 160 °C, 3d (78%); (e) PMBCl, NaH, DMF, RT, 3 h (50%); (f) MeOH, *p*TsOH, RT, 4.5 h (98%); (g) I_2, PPh_3, Imd, PhMe, 70 °C, 1 h (93%); (h) BzCl, RT, Py, 12 h (96%); (i) NBS, $CaCO_3$, CCl_4, (43%); (j) DBU, PhMe, 96 °C, 15 h (60%).

Compound **9** was readily available in 73% yield from methyl α-D-glucopyranoside by acid catalyzed acetal exchange with α,α-dimethoxytoluene in DMF.[25] Subsequent regioselective monotosylation at C-2 with either Bu_2SnO[26] (82% after chromatographic purification) or with tosylimidazole and MeONa[27] (56% after recrystallization of the crude product) gave **10**,[28] which was benzylated to afford **11**[29a] as a white crystalline solid (87%). Attempts to directly introduce a PMB (*p*-methoxybenzyl) protecting group on the C-2 hydroxy group of **9**, followed by benzylation at C-3 gave a mixture of regioselective protection with PMBCl. Instead, a stepwise approach had to be used, involving removal of tosyl group of **11** with $NaBH_4$ in DMSO[29a] (78% yield for **11a**[29b]), and then introduction of a *p*-methoxybenzyl group to yield **11b**[30] in 50%. Due to the low yield of the stepwise route, we chose to use the tosylated product **11** in further reactions.

Next, we needed a halogen group at C-6 to prepare the enone **15** (Scheme 4) for a Ferrier reaction leading to a cyclohexane skeleton. Initially, we submitted benzylidene **11** to Hannessian's protocol (NBS, $BaCO_3$, CCl_4)[31] to provide directly the bromine analogue **14a** having a benzoyl group at C-4 in one step (Scheme 4). After conventional dehydrobromination of **14a**, the resulting enone **15** would be suitable to furnish cyclitol **16** by a Ferrier reaction. Unfortunately, product recovery was not efficient since chromatographic purification caused extensive losses and compound **14a** could be isolated in 43% yield only (Scheme 4).

Consequently, an alternative route to **15** was achieved by removing first the temporary benzylidene group of **11** with *p*TsOH in MeOH.[32] The resulting diol **12** was then submitted to selective iodination at the less hindered primary hydroxyl group using PPh_3–I_2–Im, according to the procedure of Garegg and Samuelsson,[33] to synthesize **13** which was benzoylated to compound **14** (87.2% yield for the three steps).

Dehydrohalogenation of **14** (or **14a**) followed by a Ferrier rearrangement with $Hg(OAc)_2$ (Scheme 5) led to the β-hydroxycyclohexanone **16** (40% yield for the two steps). This last step needed a facile purification to separate the two epimers α and β. The axial orientation of the hydroxyl group in **16** was elucidated through the coupling constant between H-2 and H-1 ($J_{2,1} = 2.5$ Hz).



Scheme 5 *Reagents and conditions*: (k) $Hg(OAc)_2$, acetone, H_2O, AcOH, 72 °C, 4 h (66%); (l) $BnONH_2$·HCl, EtOH, pyridine, RT, 2 h (82%); (m) $Me_4NBH(OAc)_3$, TFA, 0 °C to RT, 2.5 h (70%); (n) DPPA, Ph_3P, DIAD, RT, 2.5 h (98%).

Synthesis of benzyloxime **17** was accomplished from **16** in 82% yield, by using *O*-benzylhydroxylamine hydrochloride in EtOH–pyridine. Once more, taking advantage of the axial position of the β-hydroxyl group at C-1, stereoselective reduction of the oximino benzylether function in **17** was achieved with TABH in TFA (entry 10), giving *trans* 1,3-benzylhydroxylamine **18** as the only detectable isomer in 69.7% yield (Scheme 5). The assignment of the absolute configuration of the newly created center at C-5 was done by ^{1}H NMR ($J_{5,6a} = 14.3$ Hz and $J_{5,6e} = 3.9$ Hz). Reaction of compound **18** under Mitsunobu conditions (DPPA, PPh_3, DIAD) for the azide incorporation at C-1, gave the fully orthogonal protected 2-deoxystreptamine **19** (98% yield). Vicinal coupling constants between H-1, H-6 and H-5 ($J_{6ax,1} = J_{6ax,5}$ 13.3 Hz and $J_{6eq,1} = J_{6eq,5}$ 2.4 Hz) account for the fact that H-1 and H-5 are both axially orientated. Thus, we have unambiguously confirmed the absolute stereochemistry of **19**.

In summary, we have developed an efficient and convenient inexpensive method to access a versatile diaminocyclitol unit present in aminoglycosides. It is now widely important to target a library of new type aminoglycoside antibiotics against drug-resistant bacteria. With the idea that 2-deoxystreptamine is a common component for most active aminoglycosides, we have focused on its straightforward synthesis with orthogonal protection. This will allow selective deprotection for further linkage with different substituents. Consequently, we have successfully investigated two short and efficient routes for the synthesis of highly polyprotected 2-deoxystreptamine derivatives (**8** and **19**), in only 7 steps (23% overall yield) and 11 steps (10.1% yield) respectively, with total control of the stereochemistry. These versatile and flexible entities can be prepared on a large scale and would be interesting scaffolds for the construction of novel molecular designs with improved antibacterial activity. Besides, in the course of our investigations into stereoselective hydride reduction of oximino benzylether with TABH, we have shown that the use of TFA instead of the usual AcOH was a necessary modification. Furthermore, the polyvalent units **8** and **19** could also be useful intermediates for the preparation of novel bioactive cyclitols, which are actually being studied.

Experimental

General experimental

Reactions were carried out in flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents used were of reagent grade. Tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone under argon immediately prior to use. Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm Merck pre-coated silica gel plates. Spots were detected under UV (254 nm) and/or by staining with acidic ceric ammonium molybdate unless otherwise noted. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by Merck, Geduran. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. ^{1}H NMR, ^{13}C NMR, COSY, NOESY, HMQC as well as HMBC spectra were measured on a Bruker Avance-300 spectrometer using an internal deuterium lock at ambient temperature. If not otherwise noted, $CDCl_3$ (7.26 ppm relative to residual $CHCl_3$) was the solvent for all NMR experiments. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, ABX = an ABX system. Chemical shifts are given in ppm and coupling constants are presented in Hz. ^{13}C NMR spectra were calibrated from the

central triplet peak, to 77.0 ppm for $CDCl_3$. Optical rotations [α] were recorded on a Polarimeter Model 341 (Perkin Elmer) at a wavelength of 589 nm and are reported as follows: $[\alpha]_D$, concentration (c in g/100 mL) and solvent. Elemental analysis were collected at the Service de microanalyse of the University Louis Pasteur of Strasbourg (France).

Methyl 3,4-di-*O*-benzoyl-6-deoxy-6-azido-2-*O*-tosyl-α-D-gluco-pyranoside (3). The glucopyranoside **1** (6.517 g; 9.17 mmol) and NaN_3 (4.256 g; 7.1 equiv.) were dissolved in dioxane (155 mL) and water (50 mL). The reaction was stirred at 110 °C for 48 h until all starting product had disappeared (tlc: AcOEt–hexane 1 : 1). The solvents were evaporated under reduced pressure and the white solid residue was then diluted with CH_2Cl_2 (100 mL) and water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed with water (3 × 50 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a white solid of **3** (5.096 g; 95.5%). Mp = 172 °C. $[\alpha]_D^{20} = +54.3$ (c 1.1 in $CHCl_3$). Elemental analysis for $C_{28}H_{27}N_3O_9S$ (581.593): Calcd. C, 57.82; H, 4.68; N, 7.22. Found: C, 57.52; H, 4.64; N, 6.79%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.9–6.9 (m, 14 H, Ar), 5.89 (dd, 1 H, $J_{3-2} = J_{3-4} = 9.7$ Hz, H-3), 5.32 (dd, 1 H, $J_{4-3} = J_{4-5} = 9.7$ Hz, H-4), 5.11 (d, 1 H, $J_{1-2} = 3.6$ Hz, H-1 β anomeric), 4.60 (dd, 1 H, $J_{2-1} = 3.6$ Hz, $J_{2-3} = 10$ Hz, H-2), 3.99 (ddd, Hx of ABX, 1 H, $J_{5-4} = 10$ Hz, $J_{5-6a} = 5.9$ Hz, $J_{5-6b} = 3.6$ Hz, H-5), 3.53 (s, 3 H, MeO), 3.39–3.37 (AB part on a degenerated ABX system, 2 H, H-6), 2.19 (s, 3 H, CH_3 of pTs). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.2 (CO), 164.9 (CO), 144.9 (Cq Ar), 133.6 (CH Ar), 133.1 (CH Ar), 132.7 (Cq Ar), 129.8 (CH Ar), 129.7 (2 × CH Ar), 128.8 (Cq Ar), 128.4 (CH Ar), 128.3 (Cq Ar), 128.1 (CH Ar), 127.6 (CH Ar), 97.8 (CH anomeric), 76.5 (CH-2), 69.9 (CH-4), 69.3 (CH-3), 68.8 (CH-5), 56.2 (MeO), 50.9 (CH_2-6), 21.6 (Me of pTs).

Preparation of the benzyloxime ether (6). Distilled pyridine (2.5 mL) was added to a solution of the hydroxyketone **5**[12a] (1 g; 0.0019 mole) and *O*-benzylhydroxylamine hydrochloride (352 mg; 1.16 equiv.) in dry ethanol (17 mL) at room temperature. The mixture was stirred for 6 h and then the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and water (30 mL). The organic layer was washed with a solution of HCl 2% (3 × 35 mL), water (2 × 30 mL), brine (10 mL), dried ($MgSO_4$) and filtered before being concentrated under reduced pressure to afford a white solid (1.123 g; 93.5%). The crude product was pure enough for the next step, but it was purified, for elemental analysis, with a chromatography column on silica gel (AcOEt–cyclohexane; 1 : 1) to give the desired oxime **6** as a crystalline white solid (92%). Mp = 152 °C. $[\alpha]_D^{20} = -15.1$ (c 1.04 in $CHCl_3$). Elemental analysis for $C_{34}H_{31}NO_9S$ (629.676): Calcd. C, 64.85; H, 4.96; N, 2.22. Found: C, 64.38; H, 5.01; N, 2.15%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.97–6.94 (m, 19 H, Ar), 5.90 (dd, 1 H, $J_{3-4} = J_{3-2} = 8.4$ Hz, H-3), 5.66 (d, 1 H, $J = 8.4$ Hz, H-4), 5.03 (s, 2 H, OCH_2Ph), 4.89 (dd, 1 H, $J_{2-3} = 8.5$, $J_{2-1} = 2.7$ Hz, H-2), 4.46 (m, 1 H, H-1), 2.97 (AB part of an ABX system, 2 H, $J_{6a-6b} = 15.3$ Hz, $J_{6a-1} = 5.4$ Hz, $J_{6b-1} = 3.3$ Hz, $\Delta\nu = 15.3$ Hz, H-6), 2.5 (broad s, 1 H, OH), 2.20 (s, 3 H, Me–Ar). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.2 (CO), 164.5 (CO), 147.8 (Cq), 145.1 (Cq), 137.2 (Cq), 133.2 (CH Ar), 132.8 (Cq), 129.9 (CH Ar), 129.8 (CH Ar), 129.1 (Cq), 128.8 (Cq), 128.5 (CH Ar), 128.3 (CH Ar), 128.2 (CH Ar), 127.9 (CH Ar), 127.6 (CH Ar), 80.5 (CH-2), 76.6 (OCH_2Ph), 71.3 (CH-4), 69.9 (CH-3), 67.4 (CH-1), 27.3 (CH_2-6), 21.6 (Me–Ar).

Preparation of the diol (7a). A precooled (0 °C) solution of $Me_4NBH(AcO)_3$ (1.379 g; 10.2 equiv.) in MeCN (1.6 mL) and AcOH (6.6 mL) was added dropwise to the β-hydroxyketone **5** (0.270 g; 0.514 mmol) dissolved in MeCN (3 mL) and AcOH (9 mL) at 0 °C. The reaction was left at ambient temperature for 1.5 h, water (30 mL) and diethyl ether (30 mL) were added and stirring was continued for 1 h. The aqueous layer was extracted with diethyl ether (2 × 15 mL) and the combined organic layers were washed with water (3 × 20 mL), sat. aq. $NaHCO_3$ (3 × 10 mL), water (2 × 20 mL), brine (15 mL) dried ($MgSO_4$), filtered and then concentrated under reduced pressure to afford a white solid (217 mg; 80.2%). The crude product was pure enough for the next step, but it can be purified with a chromatography column on silica gel (AcOEt–cyclohexane; 1 : 1) to give the desired diol **7a** as a crystalline white solid. Mp = 206 °C. $[\alpha]_D^{20} = -14.6$ (c 1.08 in $CHCl_3$). Elemental analysis for $C_{27}H_{26}O_9S$ (526.554): Calcd. C, 61.59; H, 4.98. Found: C, 61.48; H, 5.15%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.86–7.84 (m, 2 H, Ar), 7.63–7.60 (m, 2 H, Ar), 7.55 (d, 2 H, $J = 8.4$ Hz, pTs), 7.48–7.40 (m, 2 H, Ar), 7.30–7.23 (m, 4 H, Ar), 6.86 (d, 2 H, $J = 8.3$ Hz, pTs), 5.88 (dd, 1 H, $J_{3-4} = J_{3-2} = 10.0$ Hz, H-3), 5.28 (dd, 1 H, $J_{4-5} = J_{4-3} = 9.7$ Hz, H-4), 4.72 (dd, 1 H, $J_{2-3} = 10.0$ Hz, $J_{2-1} = 2.8$ Hz, H-2), 4.53 (m, 1 H, H-1), 4.37 (ddd, 1 H, $J_{5-6ax} = 14.2$ Hz, $J_{5-4} = 9.7$ Hz, $J_{5-6eq} = 4.7$ Hz, H-5), 2.57 (br s, 2 H, 2 × OH), 2.47 (ddd, 1 H, $J_{6eq-6ax} = 14.2$ Hz, $J_{6eq-5} = J_{6eq-1} = 4.6$ Hz, H-6eq), 2.13 (s, 3 H, Me–Ar), 1.77 (ddd, 1 H, $J_{6ax-6eq} = J_{6ax-5} = 14.2$ Hz, $J_{6ax-1} = 2.3$ Hz, H-6ax). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 166.6 (CO), 165.1 (CO), 144.9 (Cq Ar), 133.3 (CH Ar), 133.0 (CH Ar), 132.7 (Cq Ar), 129.8 (CH Ar), 129.7 (2 × CH Ar), 128.9 (Cq Ar), 128.8 (Cq Ar), 128.3 (CH Ar), 128.1 (CH Ar), 127.5 (CH Ar), 82.0 (CH-2), 77.1 (CH-4), 69.5 (CH-3), 67.7 (CH-1), 66.8 (CH-5), 35.0 (CH_2-6), 21.6 (Me–Ar).

Preparation of the benzylamine (7b). A cold solution (0 °C) of $Me_4NBH(AcO)_3$ (4.79 g; 10.2 equiv.) and TFA (12 mL) in acetonitrile (11 mL) was added to a solution of the benzyl oximine **6** (1.122 g; 1.78 mmole) in acetonitrile (20 mL) and TFA (8 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h and then poured into a vigorously stirred ice cold solution (0 °C) of water (50 mL) and diethyl ether (60 mL). The aqueous layer was neutralized with an aqueous solution of KOH. The organic layer was washed with water (3 × 50 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a white solid of the title compound **7b** (1.055 g; 93.7%). This crude product was pure enough for the next step, but it can be purified with a chromatography column on silica gel (AcOEt–cyclohexane; 4 : 6) to give the desired amine **7b** as a crystalline white solid, or recrystallized with CH_2Cl_2–diethyl ether (1 : 10), in 89.1%. Mp = 161 °C (diethyl ether). $[\alpha]_D^{20} = +34.4$ (c 1.06 in $CHCl_3$). Elemental analysis for $C_{34}H_{33}NO_9S$ (631.692): Calcd. C, 64.65; H, 5.27; N, 2.22. Found: C, 64.86; H, 5.29; N, 1.99%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.83–6.84 (m, 19 H, Ar), 5.86 (dd, 1 H, $J_{3-4} = J_{3-2} = 9.9$ Hz, H-3), 5.62 (dd, 1 H, $J_{4-5} = J_{4-3} = 10.0$ Hz, H-4), 4.70 (s, 2 H, OCH_2Ph), 4.65 (dd, 1 H, $J_{2-3} = 9.9$ Hz, $J_{2-1} = 2.7$ Hz, H-2), 4.56 (m, 1 H, H-1), 3.74 (m, 1 H, H-5), 2.88 (br s, 2 H, OH and NH), 2.38 (ddd, 1 H, $J_{6eq-6ax} = 14.4$ Hz, $J_{6eq-5} = J_{6eq-1} = 4.0$ Hz, H-6eq), 2.12 (s, 3 H, Me–Ar), 2.03 (ddd, 1 H, $J_{6ax-6eq} = 14.5$ Hz, $J_{6ax-5} = 12.2$ Hz, $J_{6ax-1} = 2.2$ Hz, H-6ax). ^{13}C NMR (75 MHz,

$CDCl_3$), δ (ppm) = 165.8 (CO), 165.1 (CO), 144.8 (Cq Ar), 136.1 (Cq Ar), 133.3 (CH Ar), 133.0 (CH Ar), 132.7 (Cq Ar), 129.7 (CH Ar), 129.6 (CH Ar), 128.9 (Cq Ar), 128.8 (Cq Ar), 128.7 (CH Ar), 128.4 (CH Ar), 128.3 (CH Ar), 128.0 (CH Ar), 127.5 (CH Ar), 81.8 (CH-2), 76.6 (OCH_2Ph), 71.0 (CH-4), 70.5 (CH-3), 67.6 (CH-1), 55.9 (CH-5), 30.3 (CH_2-6), 21.5 (Me–Ar).

Preparation of the phosphate ester (7c). To a cold solution (0 °C) of the amino alcohol **6** (160 mg; 0.253 mmole) in dry THF (1 mL) were added successively DPPA (0.1 mL; 1.8 equiv.) and DBU (0.1 mL; 2.64 equiv.). The reaction mixture was stirred at room temperature for 10 h until no more starting material was detected by tlc. The heterogeneous solution was diluted with AcOEt (10 mL) and water (10 mL) and the organic layer was washed with water (2 × 10 mL), aq. HCl 1 M (5 mL), water (10 mL), brine (5 mL), dried ($MgSO_4$), filtered and evaporated under vacuum to afford a crude product of **7c**, which was recrystallized in diethyl ether (155 mg; 71%). Mp = 138–140 °C (diethyl ether). $[\alpha]_D^{20} = +44.8$ (*c* 1 in $CHCl_3$). Elemental analysis for $C_{46}H_{42}NO_{12}PS$ (863.863): Calcd. C, 63.96; H, 4.90; N, 1.62. Found: C, 63.49; H, 4.99; N, 1.62%. ^{31}P NMR (121.5 MHz, $CDCl_3$), δ (ppm) = −11.8. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.86–6.86 (m, 29 H, Ar), 5.85 (dd, 1 H, $J_{3-4} = J_{3-2} = 9.9$ Hz, H-3), 5.63 (dd, 1 H, $J_{4-5} = J_{4-3} = 9.9$ Hz, H-4), 5.31 (m, 1 H, H-1), 4.74 (ddd, 1 H, $J_{2-3} = 10.0$ Hz, $J_{2-1} = {}^4J_{2\text{-P}} = 2.9$ Hz, H-2), 4.62 (s, 2 H, OCH_2Ph), 3.38 (m, 1 H, H-5), 2.49 (ddd, 1 H, $J_{6eq\text{-}6ax} = 15.2$ Hz, $J_{6eq\text{-}5} = J_{6eq\text{-}1} = 3.9$ Hz, H-6eq), 2.17 (s, 3 H, Me–Ar), 2.07 (m, 1 H, H-6ax). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.6 (CO), 165.1 (CO), 150.5 (Cq Ar), 150.4 (Cq Ar), 144.8 (Cq Ar), 133.3 (CH Ar), 133.0 (CH Ar), 132.8 (Cq Ar), 129.9 (CH Ar), 129.8 (CH Ar), 129.7 (CH Ar), 129.1 (Cq Ar), 129.0 (Cq Ar), 128.6 (CH Ar), 128.4 (CH Ar), 128.3 (CH Ar), 128.1 (CH Ar), 128.0 (CH Ar), 127.7 (CH Ar), 125.6 (CH Ar), 125.5 (CH Ar), 120.5 (CH Ar), 120.4 (CH Ar), 120.3 (CH Ar), 78.1 (CH-2, $J_{C-P} = 6$ Hz), 76.8 (OCH_2Ph), 75.7 (CH-1, $J_{C-P} = 9$ Hz), 71.0 (CH-4), 70.1 (CH-3), 56.1 (CH-5), 30.5 (CH_2-6), 21.6 (Me–Ar).

Preparation of the azide (8). To a cold solution (0 °C) of the alcohol **7b** (185 mg; 0.292 mmole) and triphenylphosphine (176 mg; 2.29 equiv.) in dry THF (3 mL) were successively added the DIAD (0.13 mL; 2.25 equiv.) and DPPA (0.14 mL; 2.21 equiv.). The mixture was stirred during 7 h at room temperature and then concentrated under reduced pressure to give a yellow liquid, which was purified by silica gel chromatography (AcOEt–cyclohexane 1 : 1) to afford the corresponding product **8** as a white solid (125 mg; 65.2%). Mp = 141–143 °C. $[\alpha]_D^{20} = +19.93$ (*c* 1.5 in $CHCl_3$). Elemental analysis for $C_{34}H_{32}N_4O_8S$ (656.704): Calcd. C, 62.18; H, 4.91; N, 8.53. Found: C, 62.39; H, 4.79; N, 8.52%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.8–7.7 (m, 4 H, arom.), 7.63 (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8.3$ Hz), 7.5–7.2 (m, 6 H, arom.), 6.97 (A of AA′BB′, 2 H, *p*Tol, $J_{AB} = 8.3$ Hz), 5.57–5.47 (m, 2 H, H-3 and H-4), 4.84 (m, 1 H, H-2), 4.64 (s, 2 H, CH_2Ph), 3.64 (m, 1 H, H-1), 3.22 (m, 1 H, H-5), 2.42 (ddd, 1 H, $J_{6eq\text{-}6ax} = 13.5$ Hz, $J_{6eq\text{-}1} = J_{6eq\text{-}5} = 4.4$ Hz, H-6eq), 2.17 (s, 3 H, Me of Ts), 1.83 (ddd as an apparent q, 1 H, $J_{6ax\text{-}6eq} = J_{6ax\text{-}1} = J_{6ax\text{-}5} = 13.3$ Hz, H-6ax). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.5 (CO), 165.2 (CO), 144.9 (Cq Ar), 136.9 (Cq Ar), 134.0 (Cq Ar), 133.3 (CH Ar), 133.1 (CH Ar), 129.9 (CH Ar), 129.7 (CH Ar), 129.5 (CH Ar), 128.9 (Cq Ar), 128.7 (CH Ar), 128.4 (CH Ar), 128.3 (CH Ar), 128.1 (CH Ar), 128.0 (CH Ar), 127.5 (CH Ar), 81.3 (CH-2), 77.0 (CH_2Ph), 71.9 (CH-3 or CH-4), 71.0 (CH-3 or CH-4), 59.5 (CH-1), 58.0 (CH-5), 30.7 (CH_2-6), 21.5 (Me of *p*Ts).

Methyl 3-*O*-benzyl-2-*O*-tosyl-α-D-glucopyranoside (12). The benzylidene **11** (1.579 g, 2.99 mmol) was left in suspension in MeOH (35 mL) with *p*TsOH (160 mg, 0.8 mmol). The solution, which gradually became homogeneous, was stirred for 4.5 h and then treated with aq. sat. $NaHCO_3$ (10 mL). The mixture was concentrated under reduced pressure, diluted with water (20 mL) and AcOEt (60 mL). The aqueous layer was extracted with AcOEt (20 mL). Then the combined organic extracts were washed with water (2 × 20 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to afford white crystals of **12** (1.28 g; 97.6%). This product was pure enough and can be used like that for the next step. Mp = 140 °C. $[\alpha]_D^{20} = +51.7$ (*c* 1.08 in $CHCl_3$). Elemental analysis for $C_{21}H_{26}O_8S$ (438.491): Calcd. C, 57.52; H, 5.98. Found: C, 57.93; H, 5.93%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.82–7.20 (m, 9 H, Ar), 4.81 (d, 1 H, $J_{1-2} = 3.6$ Hz, H-1), 4.64 and 4.47 (AB system, 2 H, $J = 11.5$ Hz, $\Delta\nu = 50.6$ Hz, $PhCH_2O$), 4.38 (dd, 1 H, $J_{2-3} = 9.6$ Hz, $J_{2-1} = 3.6$ Hz, H-2), 3.75 (m, 3 H, H-3 and H-6), 3.56 (m, 2 H, H-4 and H-5), 3.34 (s, 3 H, MeO), 2.40 (s, 3 H, Me of *p*Ts), 2.27 (d, 1 H, $J_{OH-4} = 2.8$ Hz, OH), 1.88 (dd, 1 H, $J_{OH-6} = 5.7$ Hz, OH). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 145.1 (Cq Ar), 137.9 (Cq Ar), 133.5 (Cq Ar), 129.8 (CH Ar), 128.6 (CH Ar), 128.0 (CH Ar), 127.9 (CH Ar), 127.8 (CH Ar), 97.7 (CH-1), 79.5 (CH-2), 78.9 (CH-3), 75.1 (OCH_2-Ph), 70.6 (CH-4 or CH-5), 70.4 (CH-4 or CH-5), 62.0 (CH_2-6), 55.5 (MeO), 21.7 (Me of *p*Ts).

Methyl 3-*O*-benzyl-6-deoxy-6-iodo-2-*O*-tosyl-α-D-glucopyranoside (13). Dry toluene (52 mL) was poured at room temperature into a mixture of the diol **12** (2.017 g; 4.59 mmole), imidazole (941 mg; 3 equiv.) and triphenylphosphine (1.35 g; 1.1 equiv.). Iodine (1.29 g; 1.1 equiv.) was then added and the deep orange solution was heated at 70 °C with vigorous stirring during 1 h. The clear reaction mixture was left at room temperature for 30 min and was then treated with aq. $NaHCO_3$ (40 mL). The organic layer was washed with water (2 × 50 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oily residue was purified on a silica gel chromatography column (diethyl ether–light petroleum ether, 1 : 1 and then AcOEt–cyclohexane, 1 : 1) to furnish the title compound **13** (2.36 g; yield 93.5%) as a white sticky solid. $[\alpha]_D^{20} = +52.4$ (*c* 1.06 in $CHCl_3$). Elemental analysis for $C_{21}H_{25}IO_7S$ (548.388): Calcd. C, 45.99; H, 4.60. Found: C, 45.67; H, 4.66%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.84–7.80 and 7.37–7.20 (m, 9 H, Ar), 4.76 (d, 1 H, $J_{1-2} = 3.6$ Hz, H-1 β anomeric), 4.69 and 4.44 (AB system, 2 H, $J = 11.5$ Hz, $\Delta\nu = 71.4$ Hz, $PhCH_2O$), 4.41 (dd, 1 H, $J_{2-3} = 9.5$ Hz, $J_{2-1} = 3.6$ Hz, H-2), 3.77 (dd, 1 H, $J_{3-2} = J_{3-4} = 9.6$ Hz, H-3), 3.36 (s, 3 H, MeO), 3.35 (m, 4 H, H-4, H-5 and H-6), 2.41 (s, 3 H, Me of *p*Ts), 2.13 (d, 1 H, $J_{OH-4} = 2.8$ Hz, OH). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 145.2 (Cq Ar), 137.8 (Cq Ar), 133.6 (Cq Ar), 129.9 (CH Ar), 128.7 (CH Ar), 128.2 (CH Ar), 128.0 (CH Ar), 127.9 (CH Ar), 97.5 (CH-1), 79.5 (CH-2), 78.5 (CH-3), 75.2 (OCH_2-Ph), 73.8 (CH-4), 69.6 (CH-5), 55.7 (MeO), 21.7 (Me of *p*Ts), 6.3 (CH_2-6).

Methyl 4-*O*-benzoyl-3-*O*-benzyl-6-deoxy-6-iodo-2-*O*-tosyl-α-D-glucopyranoside (14). Benzoyl chloride (0.5 mL; 1.07 equiv.) was added at room temperature to a solution of the alcohol **13** (2.204 g; 4.02 mmole) in pyridine (10 mL) and stirred for 12 h. Diethyl ether

(60 mL) was then added and stirring was continued for 20 min. The precipitate was filtered and thoroughly washed with diethyl ether, diluted in CH_2Cl_2 (20 mL), washed with water (2 × 15 mL) to eliminate the pyridinium salt, dried over $MgSO_4$ and concentrated under reduced pressure to afford a first crop of **14** (1.351 g; 51.5%) as a white powder, which was clean enough according the NMR analysis and needed no more purification. The previous combined ether layers were washed with water (20 mL), diluted HCl 10% (4 × 25 mL), water (2 × 25 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow solid, which was diluted in some CH_2Cl_2 and recrystallized in diethyl ether to give a second crop of colourless prisms (1.16 g; 44.2%) The total yield of the two crops was 2.51 g; 95.6%. Mp = 165 °C. $[\alpha]_D^{20} = -2.40$ (*c* 1.04 in $CHCl_3$). Elemental analysis for $C_{28}H_{29}IO_8S$ (652.494): Calcd. C, 51.54; H, 4.48. Found: C, 52.51; H, 4.57%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 8.17–6.9 (m, 14 H, Ar), 5.09 (dd, 1 H, $J_{4-3} = J_{4-5} = 9.3$ Hz, H-4), 4.97 (d, 1 H, $J_{1-2} = 3.6$ Hz, H-1 β anomeric), 4.45 (dd, 1 H, $J_{2-3} = 9.5$ Hz, $J_{2-1} = 3.6$ Hz, H-2), 4.48 and 4.39 (AB system, 2 H, $J = 11.1$ Hz, $\Delta\nu = 26$ Hz, $PhCH_2O$), 4.07 (dd, 1 H, $J_{3-2} = J_{3-4} = 9.3$ Hz, H-3), 3.86 (X of ABX, H-5), 3.49 (s, 3 H, OMe), 3.19 (AB part of an ABX system, 2 H, $J_{6a-6b} = 10.9$ Hz, $J_{6a-1} = 8.8$ Hz, $J_{6b-1} = 2.5$ Hz, $\Delta\nu = 35$ Hz, H-6), 2.35 (s, 3 H, Me-Ts). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.1 (CO), 145.1 (Cq Ar), 137.2 (Cq Ar), 133.6 (CH Ar), 133.1 (Cq Ar), 129.9 (CH Ar), 129.8 (CH Ar), 128.9 (Cq Ar), 128.5 (CH Ar), 128.1 (CH Ar), 128.0 (CH Ar), 127.8 (CH Ar), 127.5 (CH Ar), 97.6 (CH-1), 79.4 (CH-2), 76.0 (CH-3), 75.2 (CH_2Ph), 73.9 (CH-4), 69.4 (CH-5), 56.1 (OMe), 21.7 (Me), 3.8 (CH_2-6).

Methyl 4-*O*-benzoyl-3-*O*-benzyl-6-deoxy-6-bromo-2-*O*-tosyl-α-D-glucopyranoside (14a). Compound **14a** was synthesized following Hanessian's protocol.[31] The crude product was purified on a silica gel chromatography column (AcOEt–cyclohexane, 4 : 6) to afford **14a** in 43% yield. Mp = 142 °C. $[\alpha]_D^{20} = -7.2$ (*c* 2.2 in $CHCl_3$). Elemental analysis for $C_{28}H_{29}BrO_8S$ (605.494): Calcd. C, 55.54; H, 4.83. Found: C, 56.58; H, 5.19%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.9–6.9 (m, 14 H, H-arom), 5.11 (dd, 1 H, $J_{4-3} = J_{4-5} = 9.6$ Hz, H-4), 4.98 (d, 1 H, $J_{1-2} = 3.6$ Hz, H-1), 4.48 and 4.38 (AB system, 2 H, $J = 11.0$ Hz, $\Delta\nu = 26$ Hz, $PhCH_2O$), 4.44 (dd, 1 H, $J_{2-3} = 9.7$ Hz, $J_{2-1} = 3.7$ Hz, H-2), 4.07 (dd, 1 H, $J_{3-2} = J_{3-4} = 9.4$ Hz, H-3), 4.02 (ddd, H part of an ABX system, 1 H, $J_{5-4} = 10.2$ Hz, $J_{5-6a} = 7.6$ Hz, $J_{5-6b} = 2.6$ Hz, H-5), 3.47 (s, 3 H, MeO), 3.39 (AB part of an ABX system, 2 H, $J_{AB} = 11.4$ Hz, $J_{AX} = 7.6$ Hz, $J_{BX} = 2.7$ Hz, $\Delta\nu = 19.4$ Hz, H-6), 2.36 (s, 3 H, Me of *p*Ts). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.1 (CO), 145.1 (Cq Ar), 137.2 (Cq Ar), 133.6 (CH Ar), 133.1 (Cq Ar), 129.9 (CH Ar), 128.9 (CH Ar), 128.5 (CH Ar), 128.0 (CH Ar), 127.8 (CH Ar), 127.5 (CH Ar), 97.6 (CH-1), 79.3 (CH-2), 76.3 (CH-3), 75.2 (OCH_2-Ph), 72.8 (CH-4), 69.2 (CH-5), 55.9 (MeO), 29.7 (CH_2-6), 21.6 (Me of *p*Ts).

Methyl 4-*O*-benzoyl-3-*O*-benzyl-6-deoxy-2-*O*-tosyl-α-D-xylo-hex-5-enopyranoside (15). A solution of the iodoglucopyranoside **14** (1.072 g; 1.64 mmol) and DBU (1.9 mL; 7.7 equiv.) was heated in dry PhMe (10 mL) during 15 h at *ca.* 96 °C. The mixture was then left for decantation at room temperature and the upper layer was concentrated and diluted with AcOEt (30 mL). The organic layer was washed with water (2 × 50 mL), an aqueous solution of thiosulfate (1.6 M; 10 mL), water (100 mL), brine (15 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a viscous orange oil. This crude material was purified with a chromatography column on silica gel (AcOEt–cyclohexane, 1 : 3) to yield a white powder of the enone **15** (0.516; 60%). Mp = 127–128 °C. $[\alpha]_D^{20} = -20.9$ (*c* 1 in $CHCl_3$). Elemental analysis for $C_{28}H_{28}O_8S$ (524.582): Calcd. C, 64.11; H, 5.38. Found: C, 63.99; H, 5.41%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 8.00–6.94 (m, 14 H, H-arom), 5.60 (ddd, 1 H, $J_{4-3} = 9.3$ Hz, $J_{4-6a} = J_{4-6b} = 2.1$ Hz, H-4), 5.05 (d, 1 H, $J_{1-2} = 3.4$ Hz, H-1), 4.74 (dd, 1 H, $J_{6a-6b} = J_{6a-4} = 2.1$ Hz, H-6a), 4.55 (dd, 1 H, $J_{6b-6a} = J_{6b-4} = 1.9$ Hz, H-6b), 4.53 (dd, 1 H, $J_{2-3} = 9.5$ Hz, $J_{2-1} = 3.4$ Hz, H-2), 4.46 (s, 2 H, CH_2Ph), 4.09 (dd, 1 H, $J_{3-4} = J_{3-2} = 9.4$ Hz, H-3), 3.47 (s, 3 H, MeO), 2.35 (s, 3 H, Me of Ts). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 164.9 (CO), 150.3 (Cq C-5), 145.2 (Cq arom.), 137.3 (Cq arom.), 133.5 (CH arom.), 132.9 (Cq arom.), 129.9 (CH arom.), 129.1 (Cq arom.), 128.5 (CH arom.), 128.1 (CH arom.), 128.0 (CH arom.), 127.8 (CH arom.), 127.6 (CH arom.), 98.5 (C-1), 97.6 (C-6), 78.9 (C-2), 76.4 (C-3), 75.0 (CH_2Ph), 71.4 (C-4), 56.0 (MeO), 21.7 (Me of Ts).

Preparation of the cyclohexanone (16). To a solution of the enone **15** (335 mg; 0.638 mmol) in acetone (19 mL) and water (8 mL) were added $Hg(OAc)_2$ (348 mg; 1.7 equiv.) and AcOH (2 mL). The reaction was refluxed at 72 °C during 4 h and then the solvents were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL) and water (10 mL). The organic layer was washed with water (2 × 10 mL), sat. $NaHCO_3$ (2 × 5 mL), water (10 mL), brine (5 mL), dried over $MgSO_4$, filtered on Celite and concentrated under reduced pressure to afford a white solid as a mixture of two products (tlc: AcOEt–cyclohexane, 1 : 1). Purification was accomplished by chromatography on a silica gel column (AcOEt–cyclohexane 1 : 1) to get the desired hydroxyketone **16** (216 g; 66.3%). Mp = 212–213 °C. $[\alpha]_D^{20} = -74$ (*c* 1 in $CHCl_3$). Elemental analysis for $C_{27}H_{26}O_8S$ (510.555): Calcd. C, 63.52; H, 5.13. Found: C, 63.54; H, 5.22%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.9–6.9 (m, 14 H, arom.), 5.51 (d, 1 H, $J_{4-3} = 9.9$ Hz, H-4), 4.87 (dd, 1 H, $J_{2-3} = 9.4$ Hz, $J_{2-1} = 2.5$ Hz, H-2), 4.65 (m, 1 H, H-1), 4.57 and 4.45 (AB system, 2 H, $J = 11.1$ Hz, $\Delta\nu = 33$ Hz, $PhCH_2O$), 4.31 (dd, 1 H, $J_{3-4} = J_{3-2} = 9.6$ Hz, H-3), 2.80 (dd, 1 H, $J_{6a-6b} = 15.2$ Hz, $J_{6a-1} = 3.8$ Hz, H-6a), 2.71 (m, 2 H, H-6b and OH), 2.36 (s, 3 H, Me of *p*Ts). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 197.1 (CO), 165.3 (COOBz), 145.4 (Cq arom.), 137.1 (Cq arom.), 133.5 (CH arom.), 132.9 (Cq arom.), 130.0 (CH arom.), 128.9 (Cq arom.), 128.4 (CH arom.), 128.2 (CH arom.), 128.0 (CH arom.), 127.7 (CH arom.), 83.3 (C-2), 79.0 (C-4), 77.2 (C-3), 75.3 (CH_2Ph), 67.5 (C-1), 42.6 (CH_2-6), 21.7 (Me of Ts).

Preparation of the benzyloxime ether (17). To a stirred solution of the ketol **16** (222 mg; 0.43 mmol) and *O*-benzylhydroxylamine hydrochloride (84 mg; 1.2 equiv.) in dry EtOH (5 mL) was added dry pyridine (0.51 mL). The mixture, which became slowly homogeneous, was concentrated under reduced pressure after 2 h (no more starting material on tlc; AcOEt–cyclohexane 1 : 1). The crude product was dissolved in CH_2Cl_2 (20 mL), washed with water (10 mL), dil. HCl 2% (3 × 5 mL), water (10 mL), brine (5 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a white solid (263 mg), which needed a further purification on a silica gel chromatography column (ether–light petroleum 4 : 1) to afford the title compound **17** (218 mg; 81.6%). Mp = 137–138 °C (diethyl ether–petroleum ether 4 : 1). $[\alpha]_D^{20} = -24.9$ (*c* 1.1

in $CHCl_3$). Elemental analysis for $C_{34}H_{33}NO_8S$ (615.692): Calcd. C, 66.33; H, 5.40; N, 2.27. Found: C, 66.14; H, 5.46; N, 2.28%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.99–7.06 (m, 19 H, aromatics), 5.55 (d, 1 H, $J_{4\text{-}3}$ = 6.0 Hz, H-4), 5.05 (s, 2 H, N-OCH_2Ph), 4.72 (dd, 1 H, $J_{2\text{-}3}$ = 6.3 Hz, $J_{2\text{-}1}$ = 2.8 Hz, H-2), 4.65 and 4.48 (AB system, 2 H, J = 11.5 Hz, $\Delta\nu$ = 50.9 Hz, $PhCH_2O$), 4.29 (m, 1 H, H-1), 4.09 (dd, 1 H, $J_{3\text{-}4} = J_{3\text{-}2}$ = 6.2 Hz, H-3), 2.91 (AB part of an ABX system, 2 H, J_{AB} = 14.5 Hz, J_{AX} = 7.8 Hz, J_{BX} = 4.1 Hz, $\Delta\nu$ = 57.1 Hz, H-6), 2.34 (s, 3 H, Me of *p*Ts), 2.33 (d, 1 H, J = 4.1 Hz, OH). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.1 (CO), 149.6 (C-5), 145.1 (Cq arom.), 137.2 (Cq arom.), 137.1 (Cq arom), 133.2 (CH arom.), 132.8 (Cq arom.), 129.9 (CH arom.), 129.8 (CH arom.), 129.5 (Cq arom.), 128.4 (CH arom.), 128.3 (CH arom.), 128.2 (CH arom.), 127.9 (CH arom.), 127.8 (CH arom.), 127.7 (CH arom.), 81.4 (C-2), 76.5 (N-OCH_2Ph), 76.1 (C-3), 74.0 (OCH_2Ph), 71.7 (C-4), 66.4 (C-1), 27.0 (CH_2-6), 21.6 (Me of *p*Ts).

Preparation of the benzylamine (18). A cold solution (0 °C) of $Me_4NBH(AcO)_3$ (799 mg; 11.3 equiv.) and TFA (1 mL) in acetonitrile (3 mL) was added to a solution of the benzyl oximine **17** (165 mg; 0.267 mmole) in acetonitrile (4 mL) and TFA (2 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2.5 h and then poured into a vigorous stirred ice cold solution (0 °C) of water (20 mL) and diethyl ether (15 mL). The aqueous layer was neutralized with an aqueous solution of KOH (2.6g/15 mL). The organic layer was washed with water (2 × 10 mL), brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid (305 mg). This crude product was purified with a chromatography column on silica gel (AcOEt–cyclohexane; 1 : 2) to afford a crystalline white solid of the amine **18**, which was recrystallized in diethyl ether to give white needles (115 mg; 69.7%). Mp = 119–120 °C (diethyl ether). $[\alpha]_D^{20}$ = +9.5 (*c* 1.1 in $CHCl_3$). Elemental analysis for $C_{34}H_{35}NO_8S$ (617.708): Calcd. C, 66.11; H, 5.71; N, 2.27. Found: C, 65.95; H, 5.89; N, 2.19%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.97–6.84 (m, 19 H, aromatics), 5.60 (broad s, 1 H, NH), 5.38 (dd, 1 H, $J_{4\text{-}3} = J_{4\text{-}5}$ = 10.0 Hz, H-4), 4.60 and 4.56 (AB system, 2 H, J = 12 Hz, $\Delta\nu$ = 2.7 Hz, $PhCH_2O$), 4.48 (m, 1 H, H-1), 4.47 (m, 1 H, H-2), 4.35 (s, 2 H, OCH_2Ph), 4.01 (dd, 1 H, $J_{3\text{-}4} = J_{3\text{-}2}$ = 9.2 Hz, H-3), 3.45 (m, 1 H, H-5), 2.63 (broad s, 1 H, OH), 2.31 (s, 3 H, Me of *p*Ts), 2.22 (ddd, 1 H, $J_{6eq\text{-}6ax}$ = 14.4 Hz, $J_{6eq\text{-}1} = J_{6eq\text{-}5}$ = 3.9 Hz, H-6eq), 1.81 (ddd, 1 H, $J_{6ax\text{-}6eq} = J_{6ax\text{-}5}$ = 14.3 Hz, $J_{6ax\text{-}1}$ = 2.1 Hz, H-6ax). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.5 (CO), 145.1 (Cq arom.), 137.5 (Cq arom.), 133.1 (CH arom.), 132.9 (Cq arom.), 129.8 (CH arom.), 129.7 (CH arom.), 128.4 (CH arom.), 128.3 (CH arom.), 128.2 (CH arom.), 127.9 (CH arom.), 127.8 (CH arom.), 127.7 (CH arom.), 127.5 (CH arom.), 127.3 (CH arom.). 84.7 (C-2), 77.5 (C-3), 76.6 (OCH_2Ph), 75.1 (OCH_2Ph), 73.3 (C-4), 67.5 (C-1), 56.2 (C-5), 30.9 (CH_2-6), 21.6 (Me of *p*Ts).

Preparation of the azide (19). The aminoalcohol **18** (64 mg; 0.103 mmole) and triphenylphosphine (65 mg; 2.39 equiv.) were dissolved in dry THF (1.5 mL). Diisopropyl azodicarboxylate (45 μL; 2.21 equiv.) and diphenylphosphoryl azide (50 μL, 2.23 equiv.) were successively added at 0 °C. The heterogeneous reaction mixture was stirred at ambient temperature for 2.5 h and then concentrated under reduced pressure to give a yellow liquid, which was directly purified by chromatography on silica gel (AcOEt–cyclohexane 1 : 1) to yield the desired product **19** as a colorless oil (65 mg; 98.1%). $[\alpha]_D^{20}$ = −10.6 (*c* 1.7 in $CHCl_3$). Elemental analysis for $C_{34}H_{34}N_4O_7S$ (642.721): Calcd. C, 63.54; H, 5.33; N, 8.72. Found: C, 61.05; H, 5.44; N, 9.18%. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) = 7.97–6.84 (m, 19 H, aromatics), 5.35 (dd, 1 H, $J_{4\text{-}3} = J_{4\text{-}5}$ = 9.8 Hz, H-4), 4.65 (dd, 1 H, $J_{2\text{-}1} = J_{2\text{-}3}$ = 9.6 Hz, H-2), 4.58 (s, 2 H, $PhCH_2O$), 4.50 and 4.35 (AB system, 2 H, J = 11 Hz, $\Delta\nu$ = 44 Hz, $PhCH_2O$), 3.63 (dd, 1 H, $J_{3\text{-}2} = J_{3\text{-}4}$ = 9.3 Hz, H-3), 3.45 (m, 1 H, H-1), 3.08 (m, 1 H, H-5), 2.36 (ddd, 1 H, $J_{6eq\text{-}6ax}$ = 13.4 Hz, $J_{6eq\text{-}1} = J_{6eq\text{-}5}$ = 2.4 Hz, H-6eq), 2.33 (s, 3 H, Me of Ts), 1.68 (ddd as an apparent q, 1 H, $J_{6ax\text{-}6eq} = J_{6ax\text{-}1} = J_{6ax\text{-}5}$ = 13.3 Hz, H-6ax). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) = 165.3 (CO), 149.8 (Cq arom.), 144.6 (Cq arom.), 137.1 (Cq arom.), 137.0 (Cq arom.), 134.6 (Cq arom.), 133.3 (CH arom.), 130.1 (CH arom.), 129.7 (CH arom.), 129.6 (CH arom.), 128.7 (CH arom.), 128.4 (CH arom.), 128.3 (CH arom.), 128.0 (CH arom.), 127.9 (CH arom.), 127.7 (CH arom.), 127.4 (CH arom.), 126.2 (CH arom.), 120.3 (CH arom.), 120.2 (CH arom.), 83.8 (C-2), 79.9 (C-3), 76.9 (OCH_2Ph), 75.2 (OCH_2Ph), 72.8 (C-4), 59.6 (C-1), 58.3 (C-5), 30.8 (CH_2-6), 21.6 (Me of *p*Ts).

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