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Some Approaches to Glycosylated Versions of Methyl β-Acarviosin

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In a first approach to a glycosylated version of 'methyl β-acarviosin', a putative inhibitor of cellulases, cellobiose was converted into a carbocyclic enone that could not be transformed into the required amine for a subsequent alkylation. Alternatively, methyl β-acarviosin itself was glycosylated at C4′, using a 'glycosynthase', to provide the 'trisaccharide' (and some 'tetrasaccharide'). Both of these molecules were effective inhibitors of various cellulases. In a related approach to a regioisomer of the above 'trisaccharide', a selectively protected derivative of 1-epivalienamine was alkylated with a carbohydrate triflate to give a 'disaccharide' that could not be glycosylated to give the desired 'trisaccharide'. Another unsuccessful approach to this molecule is also reported.

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We have reported a synthesis of 'methyl β-acarviosin' **1**, a diastereoisomer of methyl acarviosin **2**, one of the degradation products from the treatment of acarbose with methanol (Diagram 1).[1,2] Much to our disappointment, the amine **1** proved to be an ineffective inhibitor of various cellulases, unlike the quite striking inhibitory action of **2** against some hydrolases that process α-D-glucosidic linkages.[2]

We have also shown that the inhibitory action of various imino sugars can be markedly improved upon by glycosylation. For example, isofagomine **3** is a weak inhibitor of a xylanase from *Cellulomonas fimi* but the glycosylated versions **4** and **5** exhibit a marked improvement in inhibition (Diagram 2).[3] It thus seemed a reasonable proposal to prepare the glycosylated methyl β-acarviosin derivative **6**, in the hope of developing an inhibitor of cellulases. As well, we included in our proposal a synthesis of the regioisomer **7**, potentially an inhibitor of 1,3:1,4-β-D-glucan hydrolases.[4]

There are two general approaches possible for a synthesis of **6**, namely the glycosylation of a properly functionalized methyl β-acarviosin or the alkylation of a suitable amine

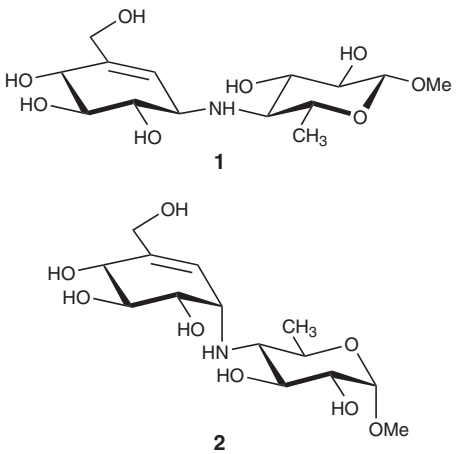

Diagram 1.

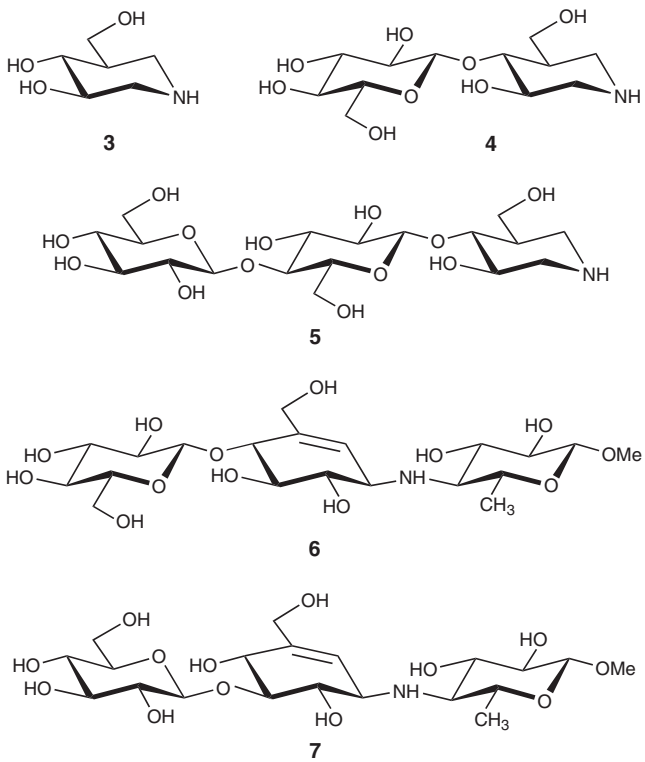

Diagram 2.

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(Diagram 3). In light of our rather inefficient synthesis of methyl β-acarviosin,[1] we chose to investigate the latter approach first.

Thus, towards an amine such as **8**, methyl β-cellobioside was converted into its benzylidene acetal and thence the iodide **9** (Scheme 1). Treatment of **9** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) then gave the alkene, and protecting group interchange provided **10**. The alkene **10** was then converted into the enone **11**.

We next needed to add a one-carbon unit to the ketone group of **11**. Treatment of **11** under a variety of conditions with the Grignard reagent derived from benzyl chloromethyl ether never yielded a single product—the diastereoisomers **12** and **13** were generally obtained in equal amounts. For **12**, there was a noticeable nuclear Overhauser effect between H5 and a H7, which was absent in **13**. The lack of stereoselectivity in this addition was both unexpected and frustrating, especially in light of a successful addition to the enone **14** (Diagram 4).[5] Still and McDonald have commented upon similar results in a related system.[6]

With small amounts of the desired diastereoisomer **12** in hand, acetylation under forcing conditions gave the acetate **15** (Scheme 1). The subsequent treatment of **15** with sodium azide under Pd(0) catalysis never realised the azide **16**, a transformation accomplished satisfactorily with the unglycosylated cyclohexene.[5]

At this stage we decided to abandon the 'amine alkylation' approach and turn to the alternative, namely the glycosylation of a methyl β-acarviosin (Diagram 3). Although conventional glycosylation methodology could be followed to achieve this aim, we had available some pure methyl β-acarviosin **1** (from our earlier synthesis) and decided to utilize an enzyme-assisted process for the glycosylation. Although glycoside hydrolases have been used extensively in the past for such glycosylations,[7] we were attracted to the obvious benefits of 'glycosynthases'.[8]

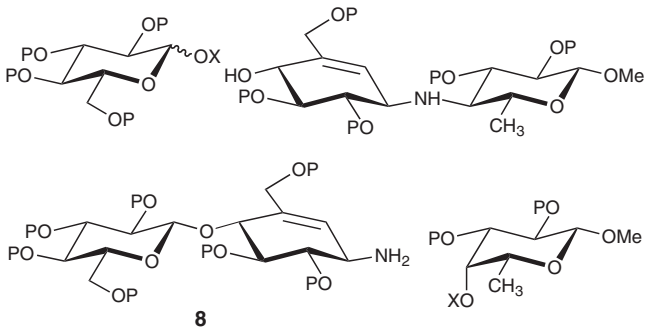

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Diagram 3.

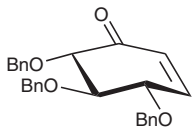

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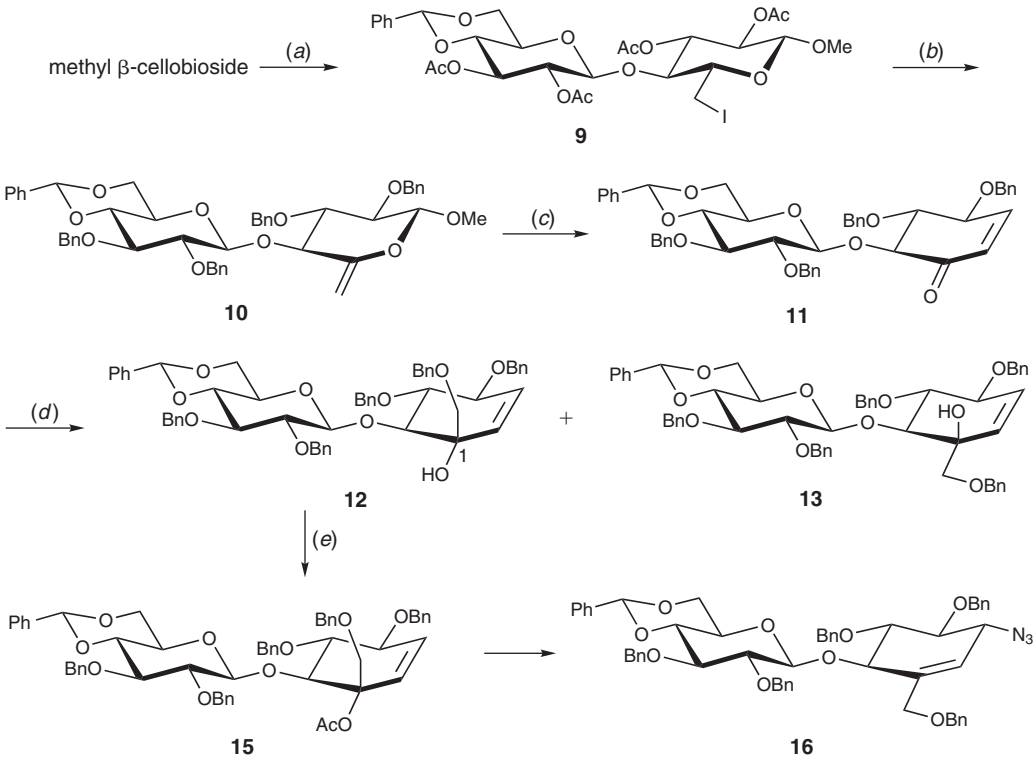
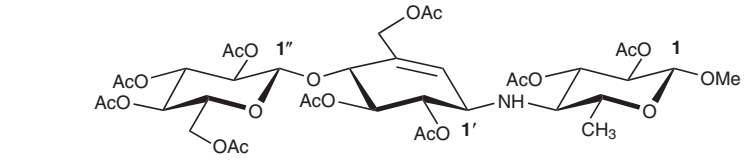
Diagram 4.



9 **10** **11** **12** **13** **15** **16**

Scheme 1. (*a*) $PhCH(OMe)_2$, PTSA, DMF, then Ph_3P, imidazole, dioxan, then Ac_2O, pyridine, DMAP; (*b*) DBU, THF, then Na, MeOH, then NaH, BnBr, DMF; (*c*) $Hg(OCOCF_3)_2$, H_2O, acetone, then MsCl, Et_3N, CH_2Cl_2; (*d*) Mg, $BnOCH_2Cl$, $HgCl_2$, THF; (*e*) Ac_2O, pyridine, DMAP.



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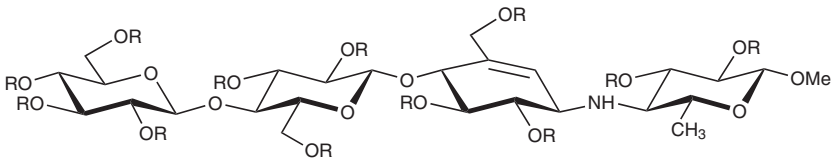

18 R = Ac
20 R = H

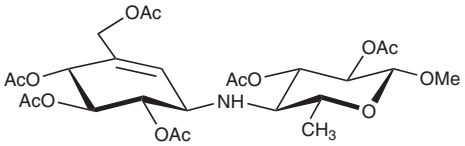

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Diagram 5.

Thus, methyl β-acarviosin **1** and α-D-glucopyranosyl fluoride in aqueous ammonium bicarbonate were treated with the glycosynthase AbgGlu358Ser.[9] After three days all of the fluoride had been consumed and the mixture appeared to contain two new compounds, isolated as their per-acetates. The major product (42%) was the 'trisaccharide' **17** (Diagram 5), along with the 'tetrasaccharide' **18** (6%) and some acetylated methyl β-acarviosin **19** (24%). The ^{1}H NMR spectrum of **17** revealed both the stereoselectivity and regioselectivity of the glycosylation—the magnitude of the coupling constant, $J_{1'',2''}$ (8.0 Hz) confirmed that a new β-D-linkage had been formed, and the chemical shift of the signal for H4′ (δ 4.20) indicated glycosylation (and not acetylation) at O4′.

The per-acetates **17** and **18** were each subjected to treatment with sodium methoxide in methanol, presumably to form the polyols **6** and **20**, and these two polyols, together with methyl β-acarviosin **1**, were assayed as inhibitors of various cellulases. The results are presented in Table 1 and, perhaps expectedly, reveal the polyol **20** to be the most effective inhibitor.

We now shifted our attention to the amine **7** and lamented the fact that there was no readily available glycoside hydrolase, let alone a glycosynthase, that could install a β-D-glucose residue at the 5′-OH of methyl β-acarviosin **1**.* Our approach had to be purely synthetic, and we chose to glycosylate the alcohol **21** (Diagram 6). This alcohol should be available from the amine **22** and the β-D-galacto triflate **23**.

A logical precursor of the amine **22** was the azide **24**, and this seemed a realistic task in view of our experiences in the synthesis of other cyclohexenyl azides from monosaccharides. Thus, in pursuit of **24**, we converted 'diacetone glucose' into its *p*-methoxybenzyl ether but methanolysis of this ether

Table 1. Inhibition constants of methyl β-acarviosin 1 and the polyols 6 and 20 against various cellulases

Cellulases	K_i [μM]		
	1	**6**	**20**
EGII (*T. reesei*)	–	–	60
CelC (*C. thermocellum*)	–	–	90
CBHII (*T. reesei*)	>1000	–	–
CBHI (*T. reesei*)	>1000	410	100
EGI (*T. reesei*)	–	200	–
CelD (*C. thermocellum*)	–	–	15

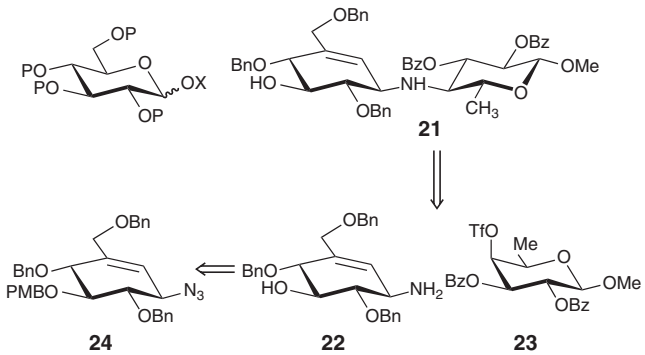


Diagram 6.

failed to give the methyl α-D-glucoside **25** (Diagram 7)—it probably gave just methyl α-D-glucopyranoside.

As an alternative, we decided to investigate the use of stannylene chemistry for the preparation of a molecule related to **25**. Although methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucoside **26** (a product of stannylene chemistry) could be converted into its *p*-methoxybenzyl ether **27**, subsequent

* Later on, such a glycosynthase did become available,[26a] but failed to couple the amine **1** and α-laminaribiosyl fluoride.[26b]

treatment with $LiAlH_4/AlCl_3$ (to transform the benzylidene ring) caused loss of the newly introduced protecting group. The selective acid hydrolysis of **27** (to remove the benzylidene group) fared no better, so we prepared the more labile *p*-methoxybenzylidene acetal **28** and attempted a selective alkylation with *p*-methoxybenzyl chloride in the presence of dibutyltin oxide—the so-formed mixture of 2- and 3-*O*-(*p*-methoxybenzyl) ethers was inseparable. Finally, we found that iodine in refluxing methanol[10] smoothly converted the ether **27** into the diol **29**.

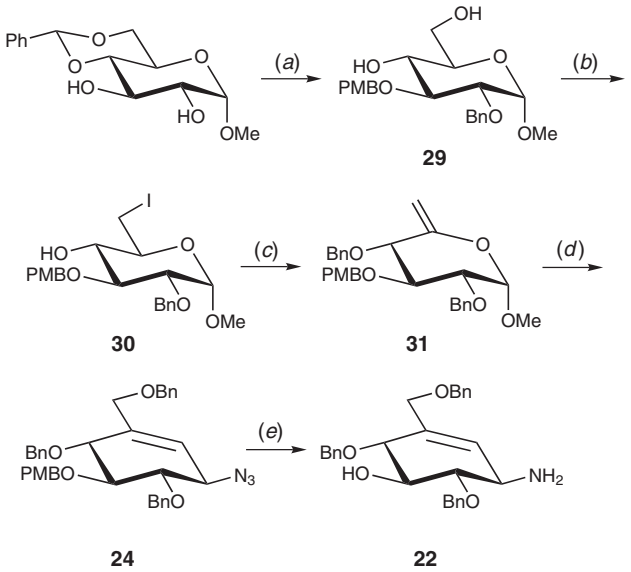
Although we gained access to **29** there was still a problem in obtaining multi-gram amounts of material—the problem resided in the selective benzylation (dibutyltin oxide, benzyl bromide, tetrabutylammonium iodide) of methyl 4,6-*O*-benzylidene-α-D-glucoside. Boons and coworkers[11,12] have reported an 83% yield for such a selective benzylation in benzene (to produce the 2-*O*-benzyl ether **26**) but we, and others, [13,14] have been unable to match this success. However, the problem was solved when we conducted the benzylation in *heptane* in the *absence* of tetrabutylammonium iodide (conditions that favour a dimeric structure for the intermediate stannylene acetal[14])—the 2-*O*-benzyl ether was isolated in 76% yield.

Returning to the synthesis of **24** (Scheme 2), the diol **29** was converted into the iodide **30** and, somewhat gratifyingly, benzylation and alkene formation proceeded in a single, subsequent step. The alkene **31** was then converted into the azide **24** in a straightforward sequence of reactions.[5] The desired amine **22** was then obtained in an oxidation–reduction sequence.

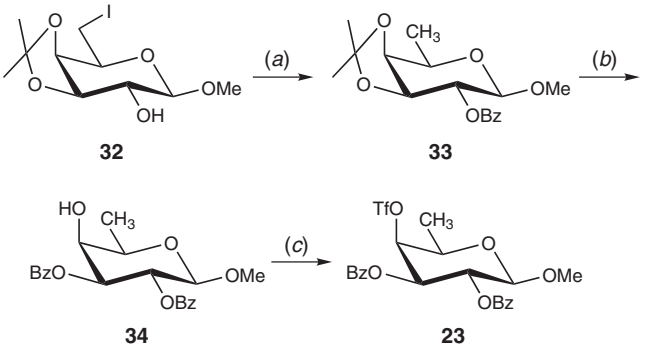
With the amine **22** in hand, we then required the triflate **23**. The iodide **32**[15] (Scheme 3) was converted into the 6-deoxy sugar **33** and subsequently the alcohol **34**. Treatment of this alcohol with triflic anhydride and pyridine then gave the crystalline and rather stable triflate **23**. Both the alcohol **34** and the triflate **23** have been prepared previously by either circuitous or poorly described routes,[16,17] and the present procedures are a vast improvement.

In the crucial alkylation step, treatment of the amine **22** with the triflate **23** gave the alcohol **21** in an acceptable yield (36%) for this sort of procedure (Scheme 4).

We were now ready for the even more crucial glycosylation step and, to our dismay, treatment of the alcohol **21** with a range of D-glucosyl donors failed to yield the desired 'trisaccharide' in pure form. Those donors tried were the bromide **35** (Diagram 8; virtually no reaction in the presence of AgOTf and tetramethylurea[18]), the trichloroacetimidate **36** (again virtually no reaction in the presence of boron trifluoride etherate; probable formation of the trimethylsilyl (TMS) ether of **21** when TMSOTf was used as the promoter; probable formation of an ortho ester, not amenable to rearrangement with TMSOTf, when AgOTf was used as the promoter),



Scheme 2. (*a*) Bu_2SnO, C_6H_6, followed by BnBr, heptane, then NaH, *p*-$MeOC_6H_4CH_2Cl$, DMF, then I_2, MeOH; (*b*) I_2, Ph_3P, imidazole, PhMe; (*c*) NaH, BnBr, DMF; (*d*) $Hg(OCOCF_3)_2$, H_2O, acetone, then MsCl, Et_3N, CH_2Cl_2, then Mg, $BnOCH_2Cl$, $HgCl_2$, THF, then Ac_2O, pyridine, DMAP, then NaN_3, $Pd(PPh_3)_4$, H_2O, THF; (*e*) DDQ, H_2O, CH_2Cl_2, then $HS(CH_2)_3SH$, Et_3N, MeOH.



Scheme 3. (*a*) H_2, Pd/C, Et_2NH, EtOAc/petrol, then BzCl, pyridine; (*b*) AcOH, H_2O, then BzCl, pyridine; (*c*) Tf_2O, pyridine, CH_2Cl_2.

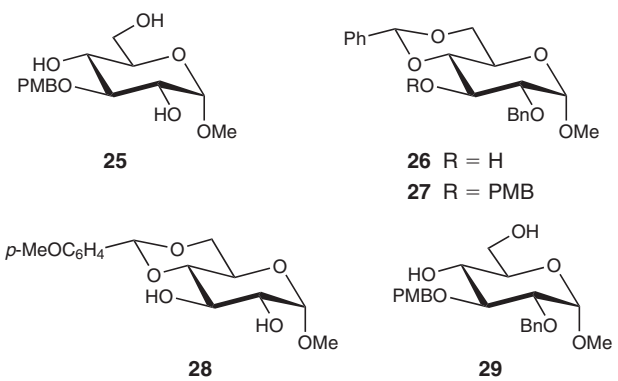
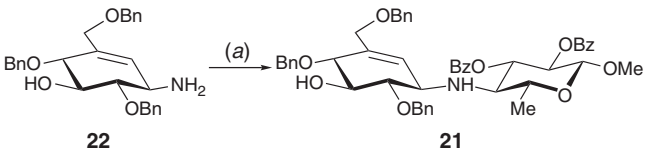


Diagram 7.



Scheme 4. (*a*) **23**, DMI.

the thioglycoside **37** (either no reaction or decomposition with varying amounts of *N*-iodosuccinmide/triflic acid as promoter), and the sulfoxide **38**.

With the sulfoxide **38** as donor, the procedure recommended by Kahne and coworkers was followed[19]—half an equivalent of triflic anhydride was added to the sulfoxide in dichloromethane at −60°C, followed by the alcohol **21**. Gratifyingly, TLC analysis of the reaction mixture showed rapid conversion of the alcohol into a new, less polar, compound. Disappointingly, though, this 'compound' proved to be an inseparable mixture of what appeared to be the two anomers of the desired 'trisaccharide'.

Although the reasons for these unsuccessful glycosylations are not clear, the answer perhaps lies in the presence of a (basic) nitrogen atom in the alcohol **21**. However, such a nitrogen atom gave no problems for Miyamoto and Ogawa (working with the validamycins)[20] and Rukhman and coworkers (glycosylating a derivative of morphine).[21] It is somewhat ironic that the very atom that seemed to be at the root of our problem is very difficult to protect—by way of example, the amine **39** is totally unreactive towards trifluoroacetic anhydride.

At this stage of our work we were very keen to follow the approach that had been first tried in pursuit of the 'trisaccharide' **6**, namely the alkylation of a regioisomer of the amine **8** (Diagram 3). Unfortunately, whereas cellobiose is a readily available disaccharide, laminaribiose is not and so a glycosylation route had to be used for the synthesis of an amine such as **40** (Diagram 9). To this end, the alcohol **41** was

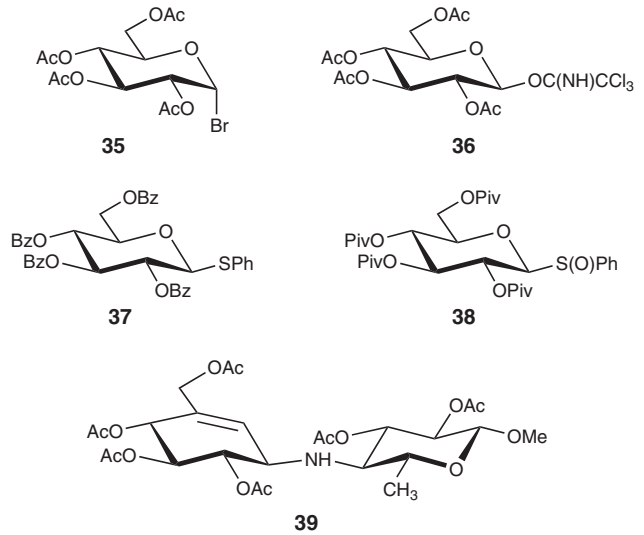


Diagram 8.

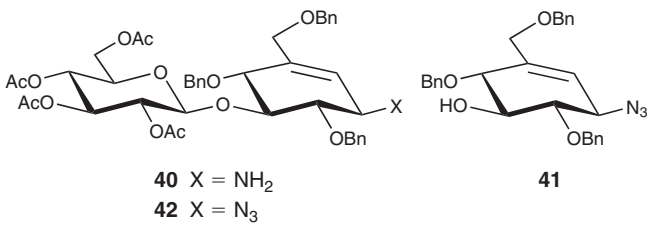


Diagram 9.

treated with the trichloroacetimidate **36** in the presence of TMSOTf—the azide **42** was formed in good yield. This success contrasts markedly with the attempts described in the paragraphs above and, no doubt, belies the absence of a (basic) nitrogen atom in the acceptor molecule.

However, our success was to be short-lived—the attempted reduction of the azide **42** to the amine **40**, using propane-1,3-dithiol in methanol, gave a complex mixture (deacetylation?), and a resultant effort to change the protecting groups of the pyranose ring (acetyl to benzyl) foundered when the sodium hydride necessary for the benzylations seemed to cause reduction of the azide group as well.

Experimental

General experimental procedures have been given previously.[5]

Methyl β-Cellobioside

Cellobiose (20 g, 58 mmol) and NaOAc (10 g) were heated in Ac_2O (180 mL) under reflux until the mixture became clear (30 min). The mixture was cooled and then poured into ice-cold water, resulting in the formation of a milky precipitate. This precipitate was collected and subjected to a normal workup (CH_2Cl_2) to give a colourless solid. This solid in HOAc (100 mL) was treated with HBr in HOAc (30% w/v, 19 mL) overnight. The solution was diluted with ice-cold water and subjected to a normal workup (CH_2Cl_2) to give an off-white solid. This solid was added to Ag_2CO_3 (12 g, 44 mmol) and powdered 3 Å molecular sieves (10 g) in MeOH (100 mL) and CH_2Cl_2 (100 mL). The resultant mixture was stirred (3 h) in the absence of light. The mixture was filtered through a plug of silica (EtOAc) and the filtrate was concentrated to give a colourless solid. A small piece of Na was added to this solid in MeOH (100 mL). Shortly afterwards, a solid began to crystallize from solution. After 1 h, the mixture was cooled and the solid collected. The filtrate was neutralized with resin [Dowex 50W-X8 (H^+)], filtered, and the filtrate concentrated to give a yellow residue. This residue and the previously collected solid were combined and recrystallized to give methyl β-cellobioside as a microcrystalline solid (13.9 g, 67%), mp 192–194°C (EtOH/MeOH; lit.[22] 198°C).

*Methyl 2,3-Di-*O*-acetyl-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucosyl)-6-iodo-β-D-glucoside* ***9***

Iodine (800 mg, 3.4 mmol) was added to methyl 4-*O*-(4,6-*O*-benzylidene-β-D-glucosyl)-β-D-glucoside (prepared from the above methyl β-cellobioside;[23] 1.0 g, 2.2 mmol), Ph_3P (890 mg, 3.4 mmol), and imidazole (460 mg, 6.8 mmol) in dioxan (5 mL). The mixture was then heated (65°C, 30 min). After the mixture was cooled, H_2O (2 mL) was added. The mixture was concentrated and the residue treated with Ac_2O/pyridine (15 mL, 1 : 2) and 4-dimethylaminopyridine (DMAP; 50 mg) for 5 h. MeOH (3 mL) was added to the mixture, which was then concentrated. Normal workup (CH_2Cl_2) gave a crystalline mass that was recrystallized to give the iodide **9** as needles (1.2 g, 72%), mp 275°C (dec.) [EtOH/$CHCl_3$; lit.[23] 268–270°C (dec.)], $[\alpha]_D$ −48.5° (lit.[23] −47.8°). δ_H (500 MHz) 2.00, 2.03, 2.03, 2.12 (4 s, 12 H, Ac), 3.23–3.30 (m, H5,6), 3.48–3.52 (m, H5′), 3.51 (s, OMe), 3.56–3.73 (m, H4, 6, 4′, 6′), 4.33–4.37 (m, H6′), 4.44 (d, $J_{1,2}$ 7.9, H1), 4.71 (d, $J_{1',2'}$ 7.8, H1′), 4.88 (dd, $J_{2,3}$ 9.5, H2), 4.94 (dd, $J_{2',3'}$ 9.2, H2′), 5.17 (dd, $J_{3,4}$ 8.9, H3), 5.28 (dd, $J_{3',4'}$ 9.3, H3′), 5.47 (s, C*H*Ph), 7.34–7.42 (m, Ph). δ_C (125 MHz) 4.25 (C6), 20.77, 20.90, 20.92 (4 C, CO*Me*), 57.01 (OMe), 66.32 (C5′), 68.36 (C6′), 71.55, 71.81, 72.57, 72.59 (C2, 3, 2′, 3′), 73.47 (C5), 77.86, 80.40 (C4, 4′), 100.92 (C1), 101.34 (C1′), 101.50 (*C*HPh), 126.05–136.52 (Ph), 169.25, 169.48, 169.61, 170.15 (4 C, C=O).

*Methyl 2,3-Di-*O*-acetyl-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucosyl)-β-D-*xylo*-hex-5-enoside*

The iodide **9** (1.0 g, 1.4 mmol) was treated with DBU (690 μL, 4.60 mmol) in THF (10 mL) at reflux (30 min). The solution was concentrated to give an orange oil. This oil was dissolved in EtOAc (40 mL)

and the resultant solution was washed with cold, aqueous HCl (1 M), followed by a normal workup to give an off-white solid. Recrystallization gave methyl 2,3-di-*O*-acetyl-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucosyl)-β-D-*xylo*-hex-5-enoside as needles (0.71 g, 86%), mp 175°C (EtOH), $[\alpha]_D$ −112° (Found C 56.6, H 5.9. $C_{28}H_{34}O_{14}$ requires C 56.5, H 5.9%). δ_H (300 MHz) 2.04, 2.06, 2.07, 2.08 (4 s, 12 H, Ac), 3.45–3.82 (m, H4′, 5′, 6′), 3.53 (s, OMe), 4.32–4.42 (m, H1, 6′), 4.62–4.68 (m, H2, 6), 4.73 (d, $J_{1',2'}$ 7.8, H1′), 4.80 (dd, $J_{4,6} \approx J_{6,6}$ 1.2, H6), 4.92 (dd, $J_{2,3} \approx J_{3,4}$ 5.1, H3), 4.98–5.07 (m, H4, 2′), 5.30 (dd, $J_{2',3'} \approx J_{3',4'}$ 9.3, H3′), 5.50 (s, C*H*Ph), 7.32–7.48 (m, Ph). δ_C (75.5 MHz) 14.54, 20.71, 20.81, 21.00 (4 C, CO*Me*), 56.99 (OMe), 65.30, 66.40, 68.47, 71.87, 72.28, 77.41, 78.05 (C2, 3, 4, 2′, 3′, 4′, 5′), 68.37 (C6′), 96.61, 100.86, 101.48 (C1, 1′, *C*HPh), 126.08–144.34 (C5, 6, Ph), 169.39, 169.44, 169.94, 170.03 (4 C, C=O).

Methyl 2,3-Di-O-*benzyl-6-deoxy-4*-O-*(2,3-di*-O-*benzyl-4,6*-O-*benzylidene-β-D-glucosyl)-β-D*-xylo-*hex-5-enoside* ***10***

A small piece of Na was added to methyl 2,3-di-*O*-acetyl-6-deoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucosyl)-β-D-*xylo*-hex-5-enoside (590 mg, 1.0 mmol) in MeOH (10 mL) at 0°C. The solution was left to stand (room temp., 1 h) and was then concentrated, co-evaporating with toluene (2 × 10 mL). NaH (220 mg, 60% dispersion in oil, 5.6 mmol) was added to a solution of the residue in dimethyl formamide (DMF; 10 mL). BnBr (520 g μL, 4.4 mmol) was then added dropwise and the resultant mixture was stirred (30 min). EtOH (1 mL) was then added. Concentration of the mixture and normal workup (CH_2Cl_2) gave a yellow oil that was purified by rapid silica filtration (RSF) (toluene to EtOAc/toluene, 1 : 3) to give the *alkene* **10** as a microcrystalline powder (760 mg, 97%), mp 93–95°C (Pr^i_2O), $[\alpha]_D$ −47° (Found C 73.2, H 6.6. $C_{48}H_{50}O_{10}$ requires C 73.3, H 6.4%). δ_H (300 MHz) δ 3.36–3.83 (m, H2, 3, 2′, 3′, 4′, 5′, 6′), 3.48 (s, OMe), 4.32 (dd, $J_{5',6'}$ 6.0, $J_{6',6'}$ 11.6, H6′), 4.43 (d, $J_{1,2}$ 6.9, H1), 4.60–4.96 (m, 12 H, H4, 6, 1′, CH_2Ph), 5.58 (s, C*H*Ph), 7.16–7.52 (m, Ph). δ_C (75.5 MHz) 56.90 (OMe), 66.00, 75.67, 80.81, 81.04, 81.20, 81.80, 82.05 (C2, 3, 4, 2′, 3′, 4′, 5′), 68.85, 73.77, 73.92, 75.21, 75.71 (5 C, C6′, *C*H_2Ph), 95.98, 100.80, 101.16 (C1, 1′, *C*HPh), 126.01–152.30 (C5, 6, Ph).

*(4*S*,5*R*,6*S*)-6-(2,3-Di*-O-*benzyl-4,6*-O-*benzylidene-β-D-glucosyloxy)-4,5-(dibenzyloxy)cyclohex-2-enone* ***11***

The alkene **10** (460 mg, 0.60 mmol) was treated with $Hg(OCOCF_3)_2$ (50 mg) in acetone/H_2O (9 mL, 2 : 1) overnight. Volatile solvents were removed and the resultant aqueous mixture was subjected to a normal workup (EtOAc), followed by RSF (EtOAc/petrol, 1 : 2), to give a colourless oil. MsCl (95 μL, 1.2 mmol) was added to this oil in Et_3N (330 μL, 2.4 mmol) and CH_2Cl_2 (10 mL) at −10°C. The solution was then left to stand (room temp., 1 h). Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 1 : 9) gave the *enone* **11** as a colourless oil (590 mg, 80%), $[\alpha]_D$ +5.7° (Found C 74.6, H 6.1. $C_{47}H_{46}O_9$ requires C 74.8, H 6.1%). δ_H (500 MHz) 3.38–3.44 (m, H5′), 3.57 (dd, $J_{1',2'}$ 7.3, $J_{2',3'}$ 8.2, H2′), 3.68 (dd, $J_{5',6'} \approx J_{6',6'}$ 10.3, H6′), 3.73 (dd, $J_{3',4'} \approx J_{4',5'}$ 9.4, H4′), 3.83 (dd, H3′), 3.94 (dd, $J_{4,5}$ 8.1, $J_{5,6}$ 10.6, H5), 4.29 (dd, $J_{5',6'}$ 5.0, H6′), 4.42 (ddd, $J_{2,4} \approx J_{3,4}$ 2.2, H4), 4.54 (d, H6), 4.73–5.13 (9H, m, H1′, CH_2Ph), 5.50 (s, C*H*Ph), 6.06 (dd, $J_{2,3}$ 10.4, H3), 6.85 (dd, H2), 7.25–7.50 (m, Ph). δ_C (125 MHz) 65.72, 78.47, 80.08, 80.72, 81.30, 82.30, 83.75 (C4, 5, 6, 2′, 3′, 4′, 5′), 69.92, 73.81, 74.77, 75.13, 75.39 (5 C, C6′, *C*H_2Ph), 101.02, 102.48 (C1′, *C*HPh), 125.98–148.24 (C2, 3, Ph), 196.01 (C1).

*(1*R*,4*S*,5*R*,6*S*)-4,5-Dibenzyloxy-1-benzyloxymethyl-6-(2,3-di*-O-*benzyl-4,6*-O-*benzylidene-β-D-glucosyloxy)cyclohex-2-en-1-ol* ***12*** *and (1*S*,4*S*,5*R*,6*S*)-4,5-Dibenzyloxy-1-benzyloxymethyl-6-(2,3-di*-O-*benzyl-4,6*-O-*benzylidene-β-D-glucosyloxy)cyclohex-2-en-1-ol* ***13***

Magnesium (370 mg, 15 mmol), benzyl chloromethyl ether (1.9 mL, 14 mmol) and $HgCl_2$ (50 mg) in THF (15 mL) were stirred (90 min, 0°C). The enone **11** (2.0 g, 2.6 mmol) was added and the mixture was stirred (1 h). The mixture was poured into saturated $NaHCO_3$ solution and the suspension was stirred (10 min). Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 15 : 85) gave, first, the alcohol **12** (900 mg, 40%) as needles, mp 124°C (Pr^i_2O), $[\alpha]_D$ +2.7° (Found C 75.0, H 6.5. $C_{56}H_{56}O_{10}$ requires C 75.2, H, 6.5%). δ_H (500 MHz) 3.16–3.24 (m, H5′), 3.24 (d, $J_{7,7}$ 9.1, H7), 3.45–3.52 (m, H2′, 6′), 3.60–3.67 (m, H7, 3′, 4′), 3.94 (dd, $J_{4,5}$ 7.2, $J_{5,6}$ 9.6, H5), 4.09 (d, H6), 4.13–4.17 (m, H4), 4.23–4.32 (m, H6′), 4.33–4.98 (10H, m, CH_2Ph), 4.39 (d, $J_{1',2'}$ 7.7, H1′), 5.52 (s, C*H*Ph), 5.63 (dd, $J_{2,3}$ 10.1, $J_{2,4}$ 2.0, H2), 5.90 (dd, $J_{3,4}$ 2.2, H3), 7.21–7.52 (m, Ph). δ_C (125 MHz) 65.81, 78.29, 78.77, 79.36, 81.46, 81.85, 81.87 (C4, 5, 6, 2′, 3′, 4′, 5′), 68.77, 72.04, 72.73, 73.20, 74.60, 74.90, 75.45 (7 C, C7, 6′, *C*H_2Ph), 72.04 (C1), 101.08, 103.25 (C1′, *C*HPh), 125.98–137.88 (C2, 3, Ph).

Next to elute was the alcohol **13** as needles (760 mg, 34%), mp 141°C (Pr^i_2O), $[\alpha]_D$ −13° (Found C 75.2, H 6.6. $C_{56}H_{56}O_{10}$ requires C 75.2, H, 6.5%). δ_H (500 MHz) 3.37–3.43 (m, H5′), 3.50–3.54 (m, H7,2′), 3.59 (d, $J_{7,7}$ 9.2, H7), 3.66 (dd, $J_{5',6'} \approx J_{6',6'}$ 10.3, H6′), 3.72 (dd, $J_{3',4'} \approx J_{4',5'}$ 9.3, H4′), 3.87 (dd, $J_{2',3'}$ 9.0, H3′), 4.03 (dd, $J_{4,5}$ 6.6, $J_{5,6}$ 10.2, H5), 4.10 (d, H6), 4.20–4.26 (m, H4, 6′), 4.24–5.00 (m, 11 H, H1′,CH_2Ph), 5.56 (s, C*H*Ph), 5.65 (dd, $J_{2,3}$ 10.4, $J_{2,4}$ 2.0, H2), 5.75 (dd, $J_{3,4}$ 2.5, H3), 7.23–7.50 (m, Ph). δ_C (125 MHz) 65.81, 78.29, 78.77, 79.36, 81.46, 81.84, 81.87 (C4, 5, 6, 2′, 3′, 4′, 5′), 68.75, 72.04, 72.73, 73.20, 74.57, 74.87, 75.45 (7 C, C7, 6′, *C*H_2Ph), 72.73 (C1), 101.08, 103.25 (C1′, *C*HPh), 125.98–137.88 (C2, 3, Ph).

*(3*R*,4*S*,5*R*,6*S*)-3-Acetoxy-5,6-dibenzyloxy-3-benzyloxymethyl-4-(2,3-di*-O-*benzyl-4,6*-O-*benzylidene-β-D-glucosyloxy)cyclohexene* ***15***

The alcohol **12** (540 mg, 0.62 mmol) was treated with Ac_2O (1 mL) and pyridine (10 mL) in the presence of DMAP (120 mg, 1.0 mmol) at 60°C for 4 h. MeOH (1 mL) was added to the now dark solution. Concentration of the mixture followed by a normal workup (EtOAc) gave a brown oil. This oil was purified by flash chromatography (EtOAc/petrol, 1 : 4) to give the acetate **15** as a colourless oil (440 mg, 79%), $[\alpha]_D$ −2.2°. δ_H (600 MHz) 1.98 (s, Ac), 3.30–3.35 (m, H5′), 3.43 (dd, $J_{1',2'}$ 7.6, $J_{2',3'}$ 8.5, H2′), 3.64 (dd, $J_{5',6'} \approx J_{6',6'}$ 10.4, H6′), 3.68 (dd, $J_{3',4'} \approx J_{4',5''}$ 9.3, H4′), 3.78 (dd, H3′), 3.82, 3.87 (2 H, ABq, *J* 10.0, H7), 4.15 (dd, $J_{4,5}$ 9.6, $J_{5,6}$ 7.4, H5), 4.26–4.32 (m, H6, 6′), 4.28–4.96 (10 H, m, CH_2Ph), 4.80 (d, H1′), 4.93 (d, H4), 5.53 (s, C*H*Ph), 5.82 (dd, $J_{1,2}$ 10.4, $J_{1,6}$ 2.4, H1), 5.89 (dd, $J_{2,6}$ 2.1, H2), 7.25–7.50 (m, Ph). δ_C (150 MHz) 22.08 (CO*C*H_3), 66.20, 77.19, 79.11, 81.28, 81.43, 81.66, 82.26 (C4, 5, 6, 2′, 3′, 4′, 5′), 68.83, 71.75, 72.24, 73.43, 74.68, 75.03, 75.07 (7 C, C7, 6′, *C*H_2Ph), 85.06 (C3), 101.06 (*C*HPh), 102.44 (C1′), 125.96–138.31 (C1, 2, Ph), 169.70 (C=O). HRMS (FAB) *m*/*z* 919.4050 [$C_{57}H_{59}O_{16}$ $(M+H)^{+\bullet}$ requires 919.4057].

*Glycosylation of Methyl 4,6-Dideoxy-4-[1′*R*,4′*R*,5′*S*,6′*S*)-4′,5′,6′-trihydroxy-3′-(hydroxymethyl)cyclohex-2′-enyl]amino-β-D-glucoside (Methyl β-Acarviosin)* ***1***

α-D-Glucopyranosyl fluoride (64 mg, 0.32 mmol) and methyl β-acarviosin **1** (80 mg, 0.23 mmol) in NH_4HCO_3 (3 mL of 0.15 M) were treated with AbgGlu358Ser (1 mg) at room temperature for 3 days. The solution was lyophilized and the resultant residue was treated with Ac_2O (1 mL) and pyridine (3 mL). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 4 : 6 to 6 : 4) gave, first, some acetylated methyl β-acarviosin[1] (32 mg, 24%), followed by the 'trisaccharide' **17** as a colourless oil (88 mg, 42%), $[\alpha]_D$ −82° (Found C 50.2, H 6.0. $C_{38}H_{54}NO_{24}$ requires C 50.2, H, 6.0%). δ_H (500 MHz) 1.33 (d, $J_{5,6}$ 6.2, 3 H, H6), 1.98, 2.00, 2.03, 2.03, 2.04, 2.05, 2.08, 2.10 (8 s, 27 H, Ac), 2.47 (dd, $J_{3,4} \approx J_{4,5}$ 9.3, H4), 3.18–3.28 (m, H5, 1′), 3.46 (s, OMe), 3.67–3.71 (m, H5″), 4.05 (dd, $J_{5'',6''}$ 2.3, $J_{6'',6''}$ 12.4, H6″), 4.20 (br d, $J_{4',5'}$ 5.7, H4′), 4.28 (d, $J_{1,2}$ 7.7, H1), 4.33 (dd, $J_{5'',6''}$ 6.6, H6″), 4.49, 4.57 (2 H, ABq, *J* 13.0, H7′), 4.68 (d, $J_{1'',2''}$ 8.0, H1″), 4.81–4.95 (m, H2, 3, 6′, 2″), 5.05 (dd, $J_{3'',4''} \approx J_{4'',5''}$ 9.4, H4″), 5.15 (dd, $J_{2'',3''}$ 9.4, H3″), 5.36 (dd, $J_{5',6'}$ 8.5, H5′), 5.84 (br s, H2′). δ_C (125 MHz) 17.78 (C6), 20.54, 20.58, 20.66, 20.69, 20.75, 20.81, 20.88 (9 C, CO*Me*), 56.75 (OMe), 56.88 (C1′), 61.64 (C6″), 62.49 (C4), 63.76 (C7′), 67.91 (C4″), 70.86 (C5′), 71.51, 71.78, 71.92, 72.09 (C2, 6′, 2″, 5″), 73.03 (C3″), 73.89 (C5), 74.82 (C3), 76.84 (C4′), 101.16 (C1), 101.43 (C1″), 128.60 (C2′), 131.16 (C3′), 169.30, 169.36, 169.54, 169.68, 170.02, 170.06, 170.26, 170.62, 171.37 (9 C, C=O).

Next to elute was the 'tetrasaccharide' **18** as a colourless oil (16 mg, 6%), $[\alpha]_D$ −28°. δ_H (600 MHz) 1.33 (d, $J_{5,6}$ 6.1, 3 H, H6), 1.97, 1.98,

2.00, 2.00, 2.07, 2.11, 2.14 (7 s, 21 H, Ac), 2.03–2.04 (m, 15 H, Ac), 2.51 (br s, H4), 3.07–3.14 (m, H5), 3.34 (br s, H1′), 3.47 (s, OMe), 3.60–3.75 (m, H4″, 5″, 5‴), 4.04 (dd, $J_{5'',6''}$ 2.2, $J_{6'',6''}$ 12.5, H6″), 4.08 (dd, $J_{5''',6'''}$ 5.5, $J_{6''',6'''}$ 12.1, H6‴), 4.19 (br s, H4′), 4.31 (br s, H7′), 4.37 (dd, $J_{5'',6''}$ 4.3, H6″), 4.39 (br d, $J_{7',7'}$ 10.8, H7′), 4.46 (d, $J_{1,2}$ 7.9, H1), 4.58 (br d, H6‴), 4.64 (br d, $J_{1'',2''}$ 7.9, H1″), 4.83–4.94 (m, H2, 3, 6′, 2″, 1‴, 2‴), 5.06 (dd, $J_{3''',4'''} \approx J_{4''',5'''}$ 9.8, H4‴), 5.13 (m, H3″,3‴), 5.33 (dd, $J_{4',5'}$ 5.7, $J_{5',6'}$ 8.4, H5′), 5.83 (br s, H2′). δ_C (150 MHz) 17.77 (C6), 20.47, 20.53, 20.59, 20.66, 20.70, 20.77, 20.81, 20.91 (12 C, CO*Me*), 56.77 (OMe), 57.00 (C1′), 61.46, 62.15, 63.74 (C7′, 6″, 6‴), 62.57 (C4), 67.69, 71.06, 71.52, 71.69, 71.87, 71.96, 72.10, 72.70, 72.81, 72.90, 73.92, 74.80, 76.34, 76.94 (C2, 3, 5, 4′, 5′, 6′, 2″, 3″, 4″, 5″, 2‴, 3‴, 4‴, 5‴), 100.88, 101.18, 101.34 (C1, 1″, 1‴), 128.61 (C2′), 131.34 (C3′), 169.14, 169.31, 169.48, 169.57, 169.69, 169.80, 169.95, 170.05, 170.21, 170.35, 170.52, 171.39 (12 C, C=O). *m/z* (FAB) 1164.3886 [$(M+H)^{+\bullet}$ requires 1164.3904].

Methyl 2-O-*Benzyl-4,6*-O-*benzylidene-α-D-glucoside* ***26***

Methyl 4,6-*O*-benzylidene-α-D-glucoside[24] (2.5 g, 8.7 mmol) and Bu_2SnO (2.4 g, 9.6 mmol) in C_6H_6 (100 mL) were heated under reflux (12 h) with the azeotropic removal of water. The now clear solution was concentrated. Heptane (50 mL) and BnBr (2.1 mL, 17 mmol) were added and the solution was heated under reflux (3 days). Concentration of the solution followed by flash chromatography (EtOAc/toluene, 1 : 9 to 3 : 17) gave, first, the alcohol **26** as a colourless solid (2.48 g, 76%), mp 129–130.5°C (EtOAc/petrol; lit.[25] 129.5°C), $[\alpha]_D$ +35° (lit.[25] +35°), followed by methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucoside, also as a colourless solid (230 mg, 7%), mp 182–183°C (EtOAc/petrol; lit.[25] 185°C), $[\alpha]_D$ +71° (lit.[25] +84°).

Methyl 2-O-*Benzyl-4,6*-O-*benzylidene-3*-O-*(4-methoxybenzyl)-α-D-glucoside* ***27***

The alcohol **26** (24.1 g, 60 mmol) was treated with NaH (3.2 g, 60% dispersion in oil, 84 mmol) and 4-methoxybenzyl chloride (10.0 mL, 72 mmol) in DMF (250 mL) for 2 h. MeOH (2 mL) was added and the mixture was concentrated to give an orange oil. This oil was subjected to a normal workup (CH_2Cl_2) to give a crystalline mass, which was used without further purification in the next step. A small portion was recrystallized to give the ether **27** as needles, mp 93°C (Pr^i_2O), $[\alpha]_D$ −33° (Found C 70.5, H 6.6. $C_{29}H_{32}O_7$ requires C 70.5, H 6.6%). δ_H (300 MHz) 3.42 (s, OMe), 3.55 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 9.6, H2), 3.58 (dd, $J_{3,4} \approx J_{4,5}$ 9.6, H4), 3.72 (dd, $J_{5,6} \approx J_{6,6}$ 9.6, H6), 3.80 (s, ArO*Me*), 3.79–3.85 (m, H5), 4.03 (dd, H3), 4.27 (dd, $J_{5,6}$ 4.7, H6), 4.60 (d, H1), 4.68–4.89 (4 H, m, CH_2Ar), 5.56 (s, C*H*Ph), 6.88–7.51 (m, 14 H, Ar). δ_C (75.5 MHz) 55.25, 55.33 (2 C, OMe), 62.34, 78.28, 79.14, 82.12 (C2, 3, 4, 5), 69.06, 73.79, 75.04 (3 C, C6, *C*H_2Ar), 99.26 (C1), 101.24 (*C*HPh), 113.72–159.18 (Ar).

Methyl 2-O-*Benzyl-3*-O-*(4-methoxybenzyl)-α-D-glucopyranoside* ***29***

The crude ether **27** was treated with I_2 (2 g) in MeOH (200 mL) at reflux (5 h). Powdered $Na_2S_2O_3$ was added. The mixture was filtered and the filtrate was concentrated to give a colourless oil. This oil was purified by flash chromatography (EtOAc/petrol, 1 : 1) to give the diol **29** as a colourless oil (22.9 g, 88% over two steps), $[\alpha]_D$ +12° (Found C 65.3, H 7.0. $C_{22}H_{28}O_7$ requires C 65.2, H 6.9%). δ_H (300 MHz) 3.36 (s, OMe), 3.36–3.62 (m, H2, 4, 5), 3.68–3.80 (3 H, m, H3, 6), 3.79 (s, ArO*Me*), 4.59 (d, $J_{1,2}$ 3.5 Hz, H1), 4.61–4.96 (4 H, m, CH_2Ar), 6.88–7.36 (m, 9 H, Ar). δ_C (75.5 MHz) 55.14, 55.20 (2 C, OMe), 70.27, 70.63, 79.71, 80.86 (C2, 3, 4, 5), 62.34, 73.09, 74.96 (3 C, C6, *C*H_2Ar), 98.13 (C1), 113.98–159.31 (Ar).

Methyl 2-O-*Benzyl-6-deoxy-6-iodo-3*-O-*(4-methoxybenzyl)-α-D-glucopyranoside* ***30***

Iodine (18.7 g, 74 mmol) was slowly added to imidazole (10.9 g, 160 mmol), Ph_3P (20.7 g, 78 mmol), and the diol **29** (22.7 g, 52.5 mmol) in toluene (200 mL). The mixture was vigorously stirred (1 h, 70°C), and then cooled and diluted with saturated $NaHCO_3$ solution (100 mL). I_2 was added until the solution remained dark (5 min). $Na_2S_2O_3$ solution (1 M) was then added to decolourize the mixture. Normal workup (toluene) followed by RSF (EtOAc/toluene, 1 : 4) gave the iodide **30** as a colourless oil (25.7 g, 87%), $[\alpha]_D$ +15° (Found C 51.5, H 5.4. $C_{22}H_{27}IO_6$ requires C 51.4, H 5.3%). δ_H (300 MHz) 3.11–3.22 (m, H2, 5), 3.32 (dd, $J_{5,6}$ 2.1, $J_{6,6}$ 9.4, H6), 3.34 (s, OMe), 3.38–3.46 (m, H4, 6), 3.65 (dd, $J_{2,3} \approx J_{3,4}$ 9.0, H3), 3.72 (s, ArO*Me*), 4.48–4.88 (4 H, m, CH_2Ar), 4.54 (d, $J_{1,2}$ 3.5, H1), 6.80–7.36 (9 H, m, Ar). δ_H (75.5 MHz) 6.98 (C6), 55.27, 55.53 (2 C, OMe), 69.78, 73.60, 79.83, 80.30 (C2, 3, 4, 5), 73.14, 74.96 (2 C, *C*H_2Ar), 98.13 (C1), 114.09–159.45 (Ar).

Methyl 2,4-Di-O-*benzyl-6-deoxy-3*-O-*(4-methoxybenzyl)-α-D*-xylo-*hex-5-enoside* ***31***

The iodide **30** (25.7 g, 46 mmol) was treated with NaH (8.0 g, 60% dispersion in oil, 200 mmol) and BnBr (7.0 mL, 65 mmol) in DMF (250 mL, 18 h). MeOH (10 mL) was added cautiously and the solution was concentrated. Normal workup (CH_2Cl_2) gave a dark oil that was purified by flash chromatography (EtOAc/petrol, 3 : 17) to give the alkene **31** as a colourless oil (16.3 g, 82%), $[\alpha]_D$ −38°. δ_H (300 MHz) 3.42 (s, OMe), 3.59 (dd, $J_{1,2}$ 3.4, $J_{2,3}$ 9.0, H2), 3.80 (s, ArO*Me*), 3.90 (ddd, $J_{3,4}$ 9.0, $J_{4,6} \approx J_{4,6}$ 1.8, H4), 4.23 (m, H3), 4.61 (d, H1), 4.65–4.87 (8 H, m, H6, CH_2Ar), 6.83–7.38 (14 H, Ar). δ_C (75.5 MHz) 55.24, 55.43 (2 C, OMe), 73.59, 75.46, 76.57 (3 C, *C*H_2Ar), 79.24, 79.51, 80.92 (C2, 3, 4), 96.77 (C6), 99.04 (C1), 113.76–159.18 (C5, Ar).

*(4*S*,5*R*,6*S*)-4,6-Dibenzyloxy-5-[(4-methoxybenzyl)oxy]-cyclohex-2-enone*

The alkene **31** (16.1 g) was treated with $Hg(OCOCF_3)_2$ (500 mg) in acetone/water (300 mL, 2 : 1) for 12 h. The mixture was concentrated somewhat and the resultant aqueous solution was extracted with CH_2Cl_2 (3 × 70 mL). The combined extracts were dried, filtered, and concentrated. RSF (EtOAc/petrol, 1 : 2) of the residue gave a colourless oil. MsCl (11 mL) was added dropwise to this oil and Et_3N (35 mL) in CH_2Cl_2 (200 mL) at −10°C. The solution was then stirred (1 h, room temp.). Normal workup (CH_2Cl_2) gave an oil that was purified by flash chromatography (EtOAc/petrol, 1 : 9 to 1 : 4) to give (4*S*,5*R*,6*S*)-4,6-dibenzyloxy-5-[(4-methoxybenzyl)oxy]cyclohex-2-enone as a colourless oil (12.0 g, 80%), $[\alpha]_D$ +62° (Found C 76.0, H 6.1. $C_{28}H_{28}O_5$ requires C 75.7, H 6.4%). δ_H (300 MHz) 3.78 (s, OMe), 3.91 (dd, $J_{4,5}$ 7.7, $J_{5,6}$ 10.7, H5), 3.99 (d, H6), 4.30 (ddd, $J_{2,4}$ 2.0, $J_{3,4}$ 2.4, H4), 4.68–5.08 (6 H, m, CH_2Ar), 5.99 (dd, $J_{2,3}$ 10.4, H3), 6.77 (dd, H2), 6.79–7.46 (14 H, m, Ar). δ_C (75.5 MHz) 55.22 (OMe), 73.57, 74.48, 75.36 (3 C, *C*H_2Ar), 78.96, 83.88, 84.31 (C4, 5, 6), 113.74–159.25 (C2, 3, Ar), 197.38 (C1).

*(1*R*,4*S*,5*R*,6*S*)-4,6-Dibenzyloxy-1-benzyloxymethyl-5-[(4-methoxybenzyl)oxy]cyclohex-2-en-1-ol*

Magnesium (4.5 g, 180 mmol), benzyl chloromethyl ether (11.0 mL) and $HgCl_2$ (200 mg) were stirred in THF (100 mL) at 0°C for 90 min. The above enone (11.8 g, 30 mmol) in tetrahydrofuran (50 mL) was added and stirring was continued at 0°C for 90 min. Saturated $NaHCO_3$ solution (100 mL) was added and the mixture left to stand (10 min). The mixture was then filtered (Celite) and the filtrate was extracted with CH_2Cl_2. The combined organic extracts were dried and filtered. Concentration of the filtrate gave an oil that was purified by flash chromatography (EtOAc/petrol, 3 : 17) to give (1*R*, 4*S*, 5*R*, 6*S*)-4,6-dibenzyloxy-1-benzyloxymethyl-5-[(4-methoxybenzyl)oxy]cyclohex-2-en-1-ol as a colourless oil (9.5 g, 64%), $[\alpha]_D$ −58° (Found C 76.2, H 7.0. $C_{36}H_{38}O_6$ requires C 76.3, H 6.8%). δ_H (300 MHz) 3.63 (d, $J_{7,7}$ 9.2, H7), 3.65–3.90 (m, H4, 5, 7), 3.81 (s, OMe), 4.18 (d, $J_{5,6}$ 6.8, H6), 4.58–4.88 (8 H, m, CH_2Ar), 5.73 (s, H2, 3), 6.81–7.42 (m, Ar). δ_C (75.5 MHz) 55.25 (OMe), 72.08, 73.08, 73.95, 74.77, 75.59 (5 C, C7, *C*H_2Ar), 75.70 (C1), 79.63, 81.27, 83.91 (C4, 5, 6), 113.72–159.15 (C2, 3, Ar).

*(3*R*,4*S*,5*R*,6*S*)-3-Acetoxy-4,6-dibenzyloxy-3-benzyloxymethyl-5-[(4-methoxybenzyl)oxy]cyclohexene*

The above alcohol (9.3 g, 16.4 mmol) was treated with Ac_2O (5.0 ml, 48 mmol) and DMAP (2.0 g, 24 mmol) in pyridine (40 mL) at 55°C for 3 h. MeOH (3 mL) was added and then the dark solution was concentrated. Normal workup (EtOAc) followed by flash chromatography (EtOAc/petrol, 1 : 9) gave (3*R*,4*S*,5*R*,6*S*)-3-acetoxy-4,6-dibenzyloxy-3-benzyloxymethyl-5-[(4-methoxybenzyl)oxy]cyclohexene as a colourless oil (8.2 g, 82%), $[\alpha]_D$ +63° (Found C 74.9, H 6.6. $C_{38}H_{40}O_7$ requires C 75.0, H 6.6%). δ_H (300 MHz) 1.86 (s, Ac), 3.80 (s, OMe), 3.88 (m, 2 H, H7), 4.07 (dd, $J_{4,5}$ 10.3, $J_{5,6}$ 7.8, H5), 4.32 (ddd, $J_{1,6}$ 2.0, $J_{2,6}$ 1.7, H6), 4.50 (d, H4), 4.56–4.89 (8 H, m, CH_2Ar), 5.83 (dd, $J_{1,2}$ 10.5, H1), 5.90 (dd, H2), 6.83–7.42 (m, Ar). δ_C (75.5 MHz) 22.02 (CO*C*H$_3$), 55.24 (OMe), 71.95, 72.24, 73.62, 74.97, 75.55 (5 C, C7, *C*H$_2$Ar), 79.93, 82.46, 85.07 (C4, 5, 6), 80.95 (C3), 113.68–159.10 (C1, 2, Ar), 170.01 (C=O).

*(3*R*,4*S*,5*S*,6*R*)-3-Azido-4,6-dibenzyloxy-1-benzyloxymethyl-5-[(4- methoxybenzyl)oxy]cyclohexene* ***24***

Tetrakis(triphenylphosphino)palladium(0) (800 mg, 0.61 mmol) was added to the above acetate (8.0 g, 13.2 mmol) and NaN_3 (5.2 g, 80 mmol) in deoxygenated THF/water (240 mL, 2 : 1). The yellow solution was heated at reflux (2 h) under Ar. Volatile solvents were removed and the resultant solution was extracted with CH_2Cl_2. The combined extracts were dried and filtered. The filtrate was concentrated to give an orange oil that was purified by flash chromatography (EtOAc/petrol, 1 : 9) to give the azide **24** as needles (4.7 g, 59%), mp 50–51°C (Et_2O/petrol), $[\alpha]_D$ −58°. δ_H (300 MHz) 3.62 (dd, $J_{3,4}$ 8.5, $J_{4,5}$ 10.5, H4), 3.80 (s, OMe), 3.83 (dd, $J_{5,6}$ 7.8, H5), 3.70 (d, $J_{7,7}$ 12.2, H7), 4.06–4.22 (m, H3,7), 4.24 (d, H6), 4.42–4.89 (8 H, m, CH_2Ar), 5.80 (br s, H2), 6.82–7.41 (m, Ar). δ_C (75.5 MHz) 55.26 (OMe), 63.52 (C3), 69.62, 72.39, 74.91, 75.14, 75.39 (5 C, C7, *C*H$_2$Ar), 79.76, 82.61, 84.05 (C4, 5, 6), 113.85–138.46 (C1, 2, Ar).

*(1*S*,2*R*,5*R*,6*S*)-5-Azido-2,6-dibenzyloxy-3-(benzyloxymethyl)-cyclohex-3-en-1-ol* ***41***

The azide **24** (4.5 g, 7.6 mmol) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 2.6 g, 11.4 mmol) in CH_2Cl_2/water (100 mL, 95 : 5) for 2 h. Normal workup (CH_2Cl_2) followed by flash chromatography (CH_2Cl_2/petrol, 2 : 3 to EtOAc/petrol, 1 : 4) gave (1*S*,2*R*,5*R*,6*S*)-5-azido-2,6-dibenzyloxy-3-(benzyloxymethyl)cyclohex-3-en-1-ol **41** as a colourless oil (2.4 g, 74%), $[\alpha]_D$ −49° (Found C 71.4, H 6.0. $C_{28}H_{29}N_3O_4$ requires C 71.3, H 6.2%). δ_H (300 MHz) 3.48 (dd, $J_{1,6}$ 10.4, $J_{5,6}$ 8.5, H6), 3.90 (dd, $J_{1,2}$ 7.8, H1), 3.98 (br d, $J_{7,7}$ 12.8, H7), 4.08–4.22 (m, H2, 5, 7), 4.47–5.02 (6 H, m, CH_2Ph), 5.65–5.69 (br s, H4), 7.22–7.45 (15 H, Ph). δ_C (75.5 MHz) 63.05 (C5), 69.54, 72.53, 74.43, 75.20 (4 C, C7, *C*H$_2$Ph), 76.13, 79.34, 82.11 (C1, 2, 6), 127.73–138.38 (C3, 4, Ph).

*(1*S*,2*R*,5*R*,6*S*)-5-Amino-2,6-dibenzyloxy-3-(benzyloxymethyl)-cyclohex-3-en-1-ol* ***22***

The azide **41** (1.25 g, 2.65 mmol) was treated with Et_3N (3.7 mL, 26 mmol) and propane-1,3-dithiol (2.9 mL, 26 mmol) in MeOH (20 mL) at reflux for 5 h. The solution was concentrated to give an orange residue that was purified by flash chromatography (EtOAc/toluene/Et_3N, 20 : 79 : 1 to EtOAc/toluene/EtOH/Et_3N, 30 : 64 : 5 : 1) to give the amine **22** as a colourless oil (1.15 g, 97%), $[\alpha]_D$ −71°. δ_H (300 MHz) 3.23 (dd, $J_{1,6}$ 9.8, $J_{5,6}$ 7.2, H6), 3.43–3.50 (m, H5), 3.92 (br d, $J_{7,7}$ 11.7, H7), 3.95 (dd, $J_{1,2}$ 9.5, H1), 4.20–4.28 (m, H2, 7), 4.48–4.93 (6 H, m, CH_2Ph), 5.62 (br s, H4), 7.21–7.42 (15 H, m, Ph). δ_C (75.5 MHz) 52.99 (C5), 70.22, 70.55, 73.99, 74.98 (4 C, C7, *C*H$_2$Ph), 76.20, 80.25, 85.23 (C1, 2, 6), 127.61–138.67 (C3, 4, Ph). *m*/*z* (FAB) 446.2346 [(M + H)$^{+\bullet}$ requires 446.2331].

*Methyl 2-*O*-Benzoyl-6-deoxy-3,4-*O*-isopropylidene-β-*D*-galactoside* ***33***

The iodide **32**[15] (2.4 g, 7.0 mmol), Et_2NH (1.5 mL, 14 mmol), and Pd-on-carbon (300 mg of 10%) were stirred overnight in EtOAc/petrol (40 mL, 1 : 1) under an atmosphere of H_2. The mixture was filtered (Celite) and the filtrate concentrated. The residue in CH_2Cl_2 (20 mL) was treated with BzCl (900 μL, 7.7 mmol) and Et_3N (2.0 mL, 14 mmol) overnight. MeOH (1 mL) was added and the solution was stirred for a further 5 min. Normal workup (CH_2Cl_2) gave a colourless solid that was taken up in Et_2O/petrol and filtered through a plug of silica. Concentration of the filtrate followed by recrystallization of the residue gave the benzoate **33** as cubes (1.6 g, 71%), mp 102–103°C (Et_2O/petrol), $[\alpha]_D$ +59°. δ_H (300 MHz) 1.35, 1.63 (2 s, CMe_2), 1.46 (3 H, d, $J_{5,6}$ 6.6, H6), 3.46 (s, OMe), 3.95 (dq, $J_{4,5}$ 2.1, H5), 4.08 (dd, $J_{3,4}$ 5.4, H4), 4.32 (dd, $J_{2,3}$ 7.4, H3), 4.59 (d, $J_{1,2}$ 8.2, H1), 5.23 (dd, H2), 7.31–7.80 (m, Ph). δ_C (75.5 MHz) 16.55 (C6), 26.38, 27.78 (*CMe*$_2$), 56.50 (OMe), 69.02, 73.60, 76.52, 77.27 (C2, 3, 4, 5), 101.38 (C1), 110.28 (*C*Me$_2$),128.24–132.96 (Ph), 165.45 (C=O).

*Methyl 2,3-Di-*O*-benzoyl-6-deoxy-β-*D*-galactopyranoside* ***34***

The benzoate **33** (580 mg, 1.8 mmol) was treated with aqueous CH_3COOH (20 mL, 80%) at 100°C for 20 min. The solution was concentrated, followed by repeated co-evaporation with toluene. The residue in CH_2Cl_2 (10 mL) was treated with BzCl (230 μL, 2.0 mmol) and pyridine (500 μL) at −50°C. The solution was allowed to warm to room temperature overnight, after which time MeOH (1 mL) was added. Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 1 : 3 to 1 : 1) gave the alcohol **34** as needles (600 mg, 86%), mp 131°C (Pr^i_2O/petrol), $[\alpha]_D$ +121° (Found C 65.4, H 5.7. $C_{21}H_{22}O_7$ requires C 65.3, H 5.7%). δ_H (300 MHz) 1.42 (d, $J_{5,6}$ 6.5, 3 H, H6), 3.53 (s, OMe), 3.89 (dq, $J_{4,5}$ 0.9, H5), 4.08–4.11 (m, H4), 4.59 (d, $J_{1,2}$ 8.0, H1), 5.30 (dd, $J_{2,3}$ 10.4, $J_{3,4}$ 3.2, H3), 5.69 (dd, H2), 7.31–7.80 (m, 10H, Ph). δ_C (75.5 MHz) 16.14 (C6), 56.82 (OMe), 69.48, 70.16, 70.55, 74.85 (C2, 3, 4, 5), 102.11 (C1), 128.28–133.36 (Ph), 165.44, 165.96 (2 C, C=O).

*Methyl 2,3-Di-*O*-benzoyl-6-deoxy-4-*O*-trifluoromethanesulfonyl-β-*D*-galactoside* ***23***

The alcohol **34** (600 mg, 1.55 mmol) was treated with Tf_2O (330 μL, 2.0 mmol) and pyridine (1 mL) in CH_2Cl_2 (10 mL) at 0°C for 20 min. The addition of saturated $NaHCO_3$ solution, followed by normal workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1 : 4), gave the triflate **23** as a microcrystalline powder (700 mg, 87%), mp 128°C (Et_2O/petrol), $[\alpha]_D$ +64°. δ_H (300 MHz) 1.48 (d, $J_{5,6}$ 6.6, 3 H, H6), 3.55 (s, OMe), 4.09 (br q, H5), 4.68 (d, $J_{1,2}$ 7.8, H1), 5.24 (br d, $J_{3,4}$ 3.0, H4), 5.57 (dd, $J_{2,3}$ 10.8, H3), 5.68 (dd, H2), 7.32–8.03 (10 H, m, Ph). δ_C (75.5 MHz) 16.40 (C6), 56.98 (OMe), 68.49, 68.86, 71.14, 84.90 (C2,3,4,5), 101.97 (C1), 118.32 (q, $J_{C,F}$ 318.9, CF_3), 128.28–133.36 (Ph), 165.01, 165.78 (2 C, C=O).

*Methyl 2,3-Di-*O*-benzoyl-4-[(1′*R*,4′*R*,5′*S*,6′*S*)-4′,6′-dibenzyloxy-3′-benzyloxymethyl-5-hydroxycyclohex-2′-enyl]amino-4,6-dideoxy-β-*D*-glucoside* ***21***

The amine **22** (1.92 g, 4.32 mmol) and the triflate **23** (900 mg, 1.74 mmol) were stirred in 1,3-dimethylimidazolidin-2-one (DMI; 3 mL) at room temperature for 4 days. The deep orange solution was concentrated (70°C, 1 mmHg) and the residue partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with more CH_2Cl_2. The combined organic extracts were dried and concentrated. Flash chromatography (EtOAc/petrol, 3 : 17 to 1 : 3) of the residue gave, first, the alcohol **21** as a pale yellow oil (520 mg, 36%), $[\alpha]_D$ −12°. δ_H (300 MHz) 1.51 (d, $J_{5,6}$ 6.5, 3 H, H6), 2.69 (br t, $J_{3,4} \approx J_{4,5}$ 9.3, H4), 3.17–3.28 (m, H1′, 6′, 7′), 3.42–3.48 (m, H5), 3.47 (s, OMe), 3.80–3.84 (2 H, m, H5′, CH_2Ph), 3.98–4.03 (m, H1, 4′, 7′), 4.58–5.10 (5 H, m, CH_2Ph), 5.34–5.46 (m, H2, 3), 5.57 (br s, H2′), 6.95–8.02 (m, Ph). δ_C (75.5 MHz) 18.12 (C6), 56.80 (OMe), 60.11, 62.96, 72.37, 74.65, 75.15, 75.67, 78.87, 82.10 (C2, 3, 4, 5, 1′, 4′, 5′, 6′), 70.53, 71.91, 73.92, 75.91 (4 C, C7′, *C*H$_2$Ph), 101.50 (C1), 127.39–138.66 (C2′, 3′, Ph), 165.32, 165.21 (2 C, C=O).

Further elution gave the amine **22** (1.30 g).

*(3*R*,4*S*,5*S*,6*R*)-3-Azido-4,6-dibenzyloxy-1-benzyloxymethyl-5-[(tetra-*O*-acetyl-β-*D*-glucopyranosyl)oxy]cyclohexene* ***42***

The alcohol **41** (180 mg, 0.39 mmol), the trichloroacetimidate **36** (380 mg, 0.78 mmol), and 4 Å molecular sieves (500 mg) were stirred in CH_2Cl_2 (5 mL) for 2 h. TMSOTf (2 drops) was added and the mixture was stirred (1 h). Solid $NaHCO_3$ (500 mg) was added and the mixture filtered through a plug of silica (EtOAc). Concentration of the filtrate, followed by flash chromatography (EtOAc/petrol, 3 : 7) of the residue, gave the D-glucoside **42** as a colourless oil (230 mg, 74%), $[\alpha]_D$ −94°. δ_H (600 MHz) 1.93, 2.01, 2.03, 2.08 (12 H, 4 s, Ac), 3.57 (dd, $J_{3,4}$ 8.6, $J_{4,5}$ 10.0, H4), 3.56–3.62 (m, H5′), 3.91 (br d, $J_{7,7}$ 12.4, H7), 4.02 (dd, $J_{5',6'}$ 2.3, $J_{6',6'}$ 12.4, H6′), 4.07–4.11 (m, H3,7), 4.19 (dd, $J_{5',6'}$ 4.5, H6′), 4.21 (br d, $J_{5,6}$ 7.4, H6), 4.23 (dd, H5), 4.43–4.97 (m, 6 H, CH_2Ph), 5.08–5.13 (m, H2′,4′), 5.17 (t, $J_{2',3'} \approx J_{3',4'}$ 9.4, H3′), 5.21 (d, $J_{1',2'}$ 8.1, H1′), 5.62 (br s, H2), 7.18–7.47 (15 H, m, Ph). δ_C (150 MHz) 20.57, 20.59, 20.60, 20.90 (4 C, CO*C*H$_3$), 61.83, 69.56, 72.64, 74.52, 75.50 (5 C, C7, 6′, *C*H$_2$Ph), 63.52, 68.27, 71.87, 71.98, 72.95, 78.00, 79.81, 82.74 (C3, 4, 5, 6, 2′, 3′, 4′, 5′), 99.80 (C1′), 122.39–138.38 (C1, 2, Ph), 169.13, 169.40, 170.21, 170.61 (4 C, C=O). HRMS m/z (FAB) 802.3198 [$(M + H)^{+\bullet}$ requires 802.3187].

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