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An Investigation into the Synthesis of Some Molecules Related to Methyl Acarviosin

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Methyl acarviosin is an impressive inhibitor of some glycoside hydrolases that process substrates containing α-D-glucosidic linkages. In an attempt to provide putative inhibitors for enzymes that process β-D-glucosidic linkages, we report an improved synthesis of a hydroxylated 'methyl β-acarviosin' and our efforts towards various deoxygenated versions of methyl β-acarviosin. As well, the synthesis of a 1,3-linked variant of methyl β-acarviosin is reported, together with an unsuccessful 'tether' approach to construct the crucial nitrogen linkage in the acarviosins.

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Acarbose **1** (Diagram 1) is an excellent inhibitor of several enzymes that process substrates containing α-D-glucosidic linkages and, as such, is used in the treatment of various forms of diabetes.[1–4] Methyl acarviosin **2**, the apparent core of acarbose, is an even better inhibitor of sucrase than acarbose itself.[5]

Some years ago, we were inspired to prepare β-acarbose **3**, in the hope that the molecule would inhibit those enzymes that process β-D-glucosidic linkages.[6,7] After a prolonged synthetic sequence, we were disappointed to find that β-acarbose was, in fact, a *substrate* for various β-glucosidases and cellulases![8] Putting this result aside, we prepared the core of β-acarbose, namely 'methyl β-acarviosin' **4**,[9] and this molecule did show some ability to inhibit the action of various β-glucosidases.[8]

Two things still seemed worthy of further investigation: (1) the synthesis of other, or further, deoxy derivatives of **4**, to probe the importance of hydrophobic contacts in binding; and (2) the glycosylation of **4** at the non-reducing terminus, to produce analogues of β-acarbose with a reduced propensity towards hydrolysis. Therefore, in the first part of these investigations, we decided to prepare the analogues **5** and **6** and, in a related approach, the 1,3-linked molecule **7**, for possible use as an inhibitor of hydrolases that process 1,3-β-D-glucosidic linkages.

Our successful synthesis of methyl β-acarviosin **4** had resulted from the alkylation of the 1-epivalienamine derivative **8** by the triflate **9**.[9] Before employing such an approach in the synthesis of the analogues **5** and **6**, we decided to improve upon our previous synthesis of the 6-hydroxylated version of methyl β-acarviosin, namely **10** (this synthesis had been rather laborious, being intimately linked with our synthesis of methyl β-adiposin-2).[10,11]

Thus, methyl β-D-galactopyranoside was converted into the alcohol **11** and thence the triflate **12** (Scheme 1).[12] The 1-epivalienamine derivative **8** was prepared according to the published procedure,[13] except that the final reduction of the azide to the amine was performed with sodium sulfide, rather than the noxious hydrogen sulfide. Treatment of **8** with the triflate **12** in 1,3-dimethylimidazolidin-2-one (DMI) then gave the amine **13** (41%), together with substantial amounts of the alkene **14** (Diagram 2) and unreacted starting materials. The deprotection of **13** (sodium in methanol, then lithium in ammonia), followed by acetylation, then yielded the heptaacetate **15**, and deacetylation gave the desired **10**.

For a synthesis of **5**, we decided to prepare the triflate **16** (Scheme 2). Thus, methyl β-D-galactopyranoside was converted into the diol **17**.[9,14] In something of a gamble, we treated the diol **17** with dibutyltin oxide in refluxing toluene, and then added *O*-phenyl chlorothioformate, in the hope of forming the thiocarbonate **18**—unfortunately, only the cyclic thiocarbonate **19** resulted (Diagram 2).

As an alternative, the diol **17** was converted into the acetate **20** and a modified Barton–McCombie deoxygenation gave the 3-deoxy derivative **21**. Deacetylation of **21** gave the alcohol **22**, treatment of which with triflic anhydride appeared to give (^{1}H NMR spectroscopy) the unstable triflate **16**. Unfortunately, **16** decomposed readily upon workup, and alkylation of the 1-epivalienamine derivative **8** proved unsuccessful. In a slight aside, the less reactive mesylate **23** was prepared but was found to be unreactive towards **8**.

Before these alkylation attempts, we had started our synthesis towards the triflate **24** (Scheme 3), a necessary precursor of the dideoxy target **6**. Thus, methyl β-D-galactopyranoside was converted into the 6-deoxy derivative **25**, and

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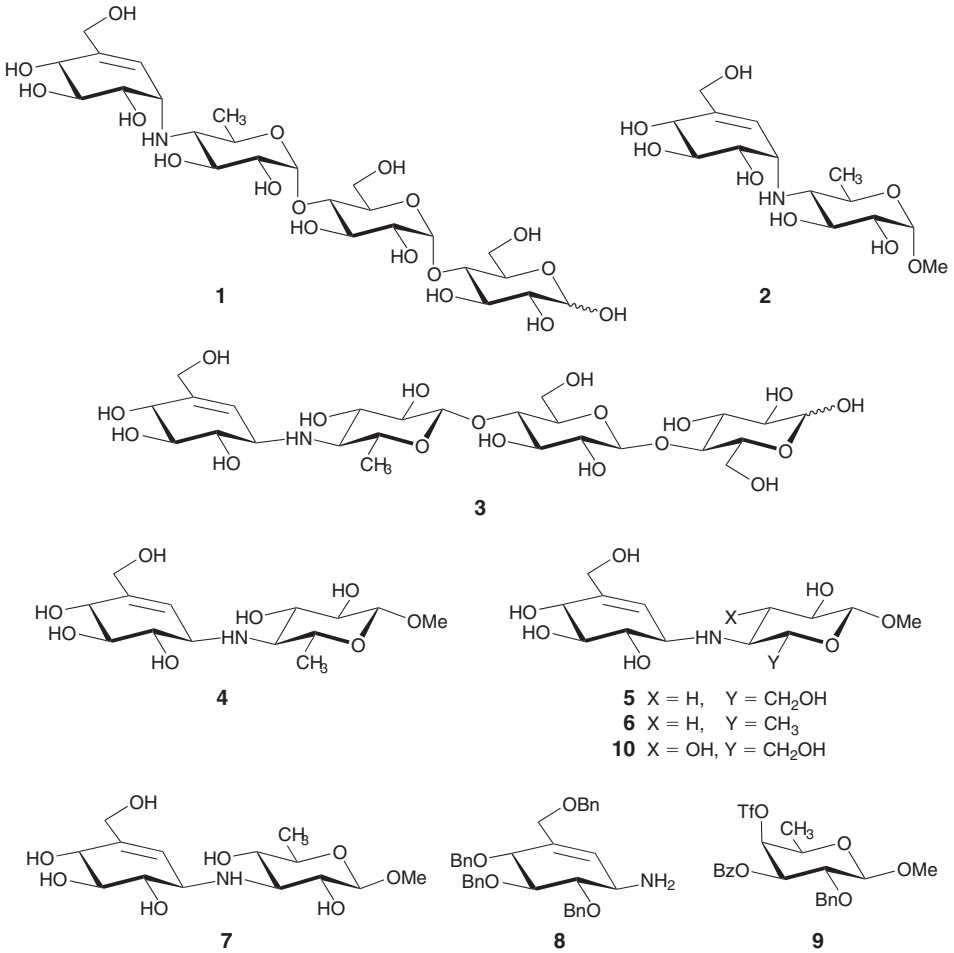
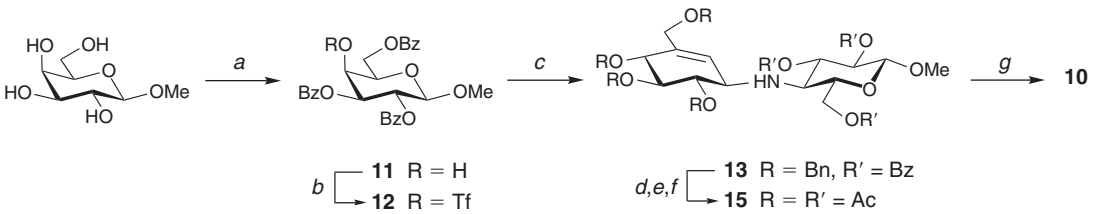


Diagram 1.



Scheme 1. (*a*) BzCl, pyridine, CH_2Cl_2, −50°C; (*b*) Tf_2O, pyridine, CH_2Cl_2, −10°C; (*c*) **8**, DMI; (*d*) Na, MeOH; (*e*) Li, NH_3, THF, −78°C; (*f*) Ac_2O, pyridine, DMAP; (*g*) Na, MeOH.

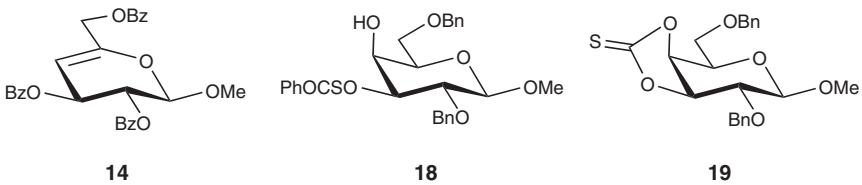
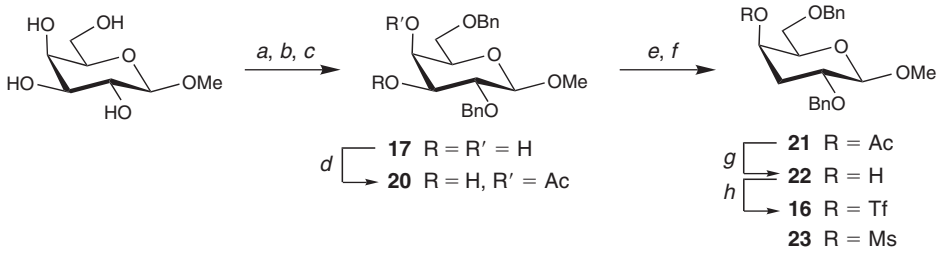


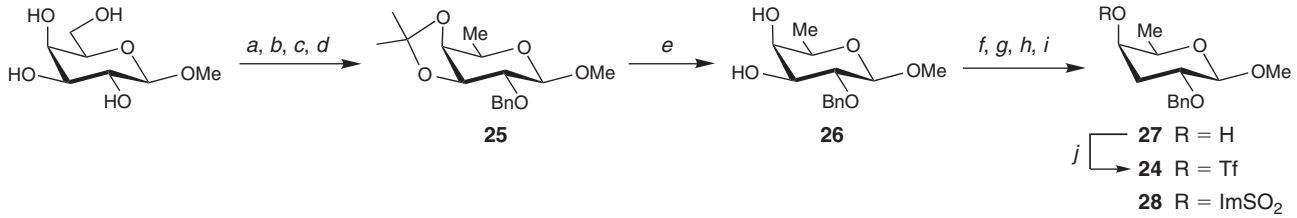
Diagram 2.

selective hydrolysis of **25** gave the diol **26**.[9] The diol **26** was then converted into the alcohol **27** in a sequence parallel to that used on the diol **17**.

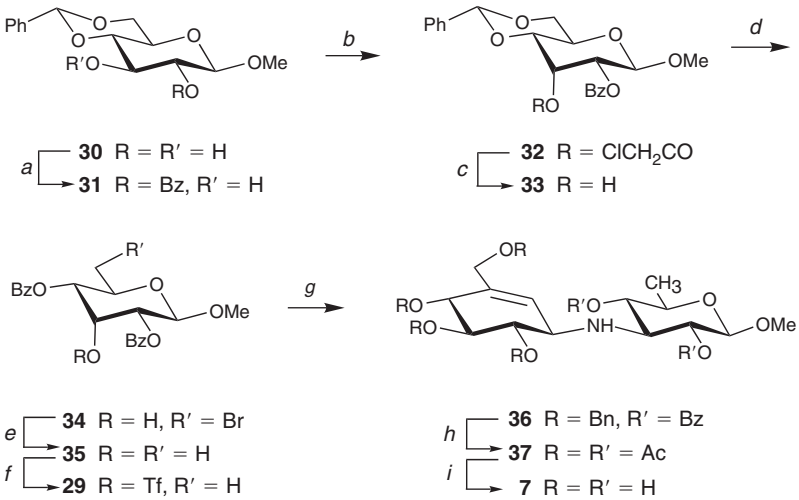
Although well aware of the instability of the triflate **16**, we still attempted the conversion of the alcohol **27** into the triflate **24**. Again, the product was a somewhat unstable oil that did not allow for a successful alkylation of the 1-epivalienamine derivative **8**. We did attempt the preparation of the 'imidazolate' **28**, generally more stable than a triflate but no less reactive,[15] but only the products of elimination



Scheme 2. (*a*) $Me_2C(OMe)_2$, camphorsulfonic acid (CSA); (*b*) BnBr, NaH, DMF; (*c*) 80% aq. AcOH, 60°C; (*d*) $MeC(OEt)_3$,$CHCl_3$, CF_3COOH, then MeCN, H_2O; (*e*) ClC(S)OPh, pyridine, CH_2Cl_2; (*f*) Bu_3SnH, AIBN, $PhCH_3$, 70°C; (*g*) Na, MeOH; (*h*) Tf_2O, pyridine, CH_2Cl_2, −50°C.



Scheme 3. (*a*) $Me_2C(OMe)_2$, CSA; (*b*) I_2, Ph_3P, imidazole, $PhCH_3$; (*c*) BnBr, NaH, DMF; (*d*) $LiAlH_4$, THF; (*e*) 80% aq. AcOH, 60°C; (*f*) $MeC(OEt)_3$, $CHCl_3$, CF_3COOH, then MeCN, H_2O; (*g*) ClC(S)OPh, pyridine, CH_2Cl_2; (*h*) Bu_3SnH, AIBN, $PhCH_3$, 70°C; (*i*) Na, MeOH; (*j*) Tf_2O, pyridine, CH_2Cl_2, −50°C. In structure **28**, Im represents imidazol-1-yl.



Scheme 4. (*a*) 1-(Benzoyloxy)benzotriazole, Et_3N, THF; (*b*) $ClCH_2CO_2H$, Ph_3P, diethyl azodicarboxylate (DEAD), THF/C_6H_6; (*c*) thiourea, 2,6-lutidine, MeOH/CH_2Cl_2, 40°C; (*d*) *N*-bromosuccinimide, $CaCO_3$, CCl_4, 77°C; (*e*) Bu_3SnH, $PhCH_3$, 70°C; (*f*) Tf_2O, pyridine, CH_2Cl_2, −20°C to room temperature; (*g*) **8**, DMI; (*h*) Na, MeOH/THF, then Na, NH_3, THF, −78°C, then Ac_2O, pyridine, DMAP; (*i*) Na, MeOH.

(alkenes) were observed when the alcohol **27** was treated with imidazolesulfonic anhydride and pyridine.

The 1,3-linked molecule **7** required the preparation of the triflate **29** (Scheme 4). Thus, the diol **30** was treated with 1-(benzoyloxy)benzotriazole[16] to give the 2-*O*-benzoyl derivative **31**; this procedure avoids the formation of any dibenzoate, and the easily separated 3-*O*-benzoyl derivative can be recycled.

The alcohol **31** was then subjected to a Mitsunobu reaction with chloroacetic acid to give the chloroacetate **32**; a selective de-esterification with thiourea then gave the D-*allo* alcohol **33**. A Hanessian–Hullar reaction on **33** gave the bromide **34**, the reduction of which produced the 6-deoxy sugar **35**. Treatment of **35** with triflic anhydride then gave the triflate **29**.

Finally, the 1-epivalienamine derivative **8** was treated with the triflate **29** in DMI to give a satisfactory yield (55%) of the amine **36**. Interestingly, and as noted before in similar systems,[6] the ^1H NMR spectrum of **36** contained several broadened signals for the (non-aromatic) ring hydrogens—this broadening was frequency-dependent (obvious at 500 MHz but not so much at 300 Hz) and clearly correlated with the NMR time scale. The origin of the line broadening probably lies in a slow inversion of configuration at the nitrogen atom, substituted with bulky/electron-withdrawing groups.[6,17]

Deprotection of the amine **36** (sodium in methanol, then sodium in ammonia), followed by acetylation, gave the hexaacetate **37**; deacetylation then gave the target **7**. The amine **7**

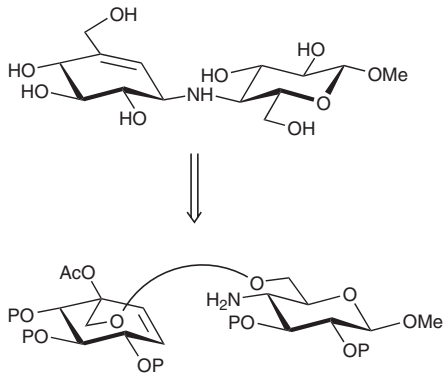


Diagram 3. P = protecting group.

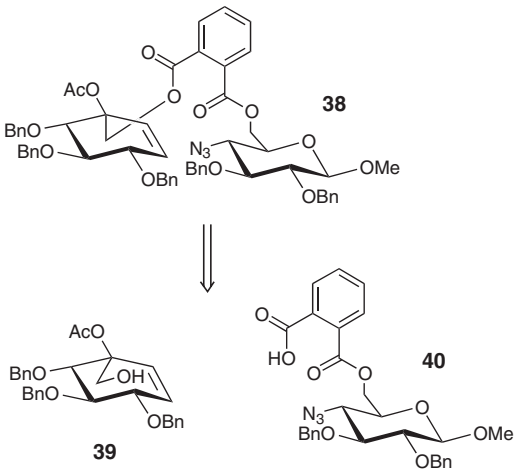


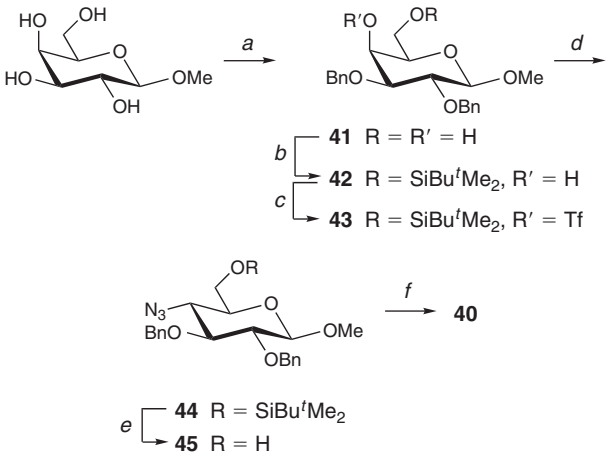
Diagram 4.

proved to be completely inactive as an inhibitor of a 1,3-β-glucanase from barley.[18]

While we were carrying out the above synthetic work, we were cognizant of the popularity of 'tether' chemistry for the synthesis of (glycosidic) linkages, pioneered by Ziegler[19] and Schmidt.[20] It seemed to us that a similar approach, utilizing well established Pd(0) chemistry,[13] could be used to construct the crucial nitrogen linkage in the acarviosins (Diagram 3). It was hoped that the tether would both control the regioselectivity and confer good stereoselectivity on the process, two features lacking in a related intermolecular alkylation by Bols.[21] The tether chosen was the stable phthalic acid diester, and the synthetic target was the azide **38**, seemingly available from the alcohol **39** and the acid **40** (Diagram 4).

Methyl β-D-galactopyranoside was easily converted into the diol **41** (Scheme 5). A selective silylation of **41** then gave the alcohol **42**, subsequently transformed into the triflate **43** and the azide **44**. The D-*gluco* configuration of **44** was confirmed by a measurement of the value of $J_{4,5}$ (9.4 Hz) in the ^{1}H NMR spectrum. Selective deprotection of **44** gave the alcohol **45**, which was esterified with phthalic anhydride to give the required acid **40**.

For the synthesis of the other partner, the alcohol **39**, the enone **46**[13] (Scheme 6) was an obvious starting point. In previous work, we had mastered the rather tricky addition of



Scheme 5. (*a*) $PhCH(OMe)_2$, CSA, DMF, 60°C, then Et_3N, then BnBr, NaH, then 80% aq. HOAc, 100°C; (*b*) Bu^tMe_2SiCl, ImH, DMF; (*c*) Tf_2O, pyridine, CH_2Cl_2, 0°C; (*d*) NaN_3, DMF, 80°C; (*e*) 80% aq. HOAc, 100°C; (*f*) phthalic anhydride, pyridine, DMAP.

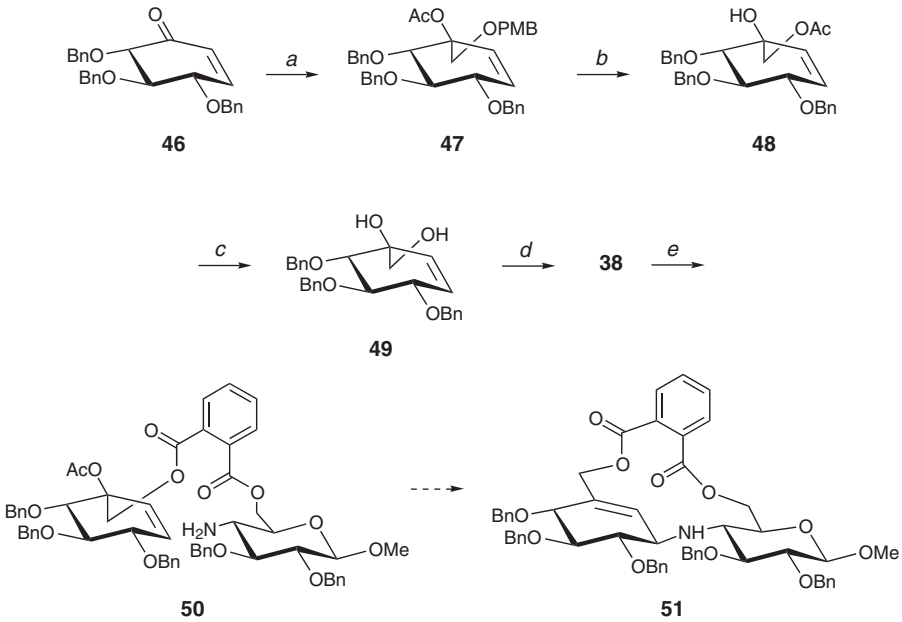
the Grignard reagent derived from benzyl chloromethyl ether to the enone **46**.[13] Here, we required a halomethyl ether that ultimately provided a protecting group in the product, orthogonal to a benzyl ether—*t*-butyl chloromethyl ether[22] and (*t*-butyldimethylsilyloxy)methyl chloride[23] were both tried but neither allowed for a successful Grignard addition to **46**.

However, with an improved preparation of chloromethyl 4-methoxybenzyl ether[24] at hand (just half an equivalent of sulfuryl chloride added to 4-methoxybenzyl methylthiomethyl ether), a successful Grignard addition to the enone **46** presumably gave the tertiary alcohol, and thence the acetate **47**. The configuration of the new stereogenic centre in **47** was not determined but predicted on the basis of a related addition to the enone **46**.[13] Treatment of the acetate **47** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) did not give the expected alcohol **39**, but instead gave rise to the isomeric **48**! The structure of the rearranged product **48** was derived from an inspection of its ^{1}H NMR spectrum and the subsequent sluggish esterification (1,3-dicyclohexylcarbodiimide/*N*,*N*-dimethylaminopyridine; DCC/DMAP) with the acid **40**.

To circumvent this result, the alcohol **48** was deacetylated and the resulting diol **49** combined with a slight molar excess of the acid **40**. TLC analysis showed complete consumption of the diol **49**, so an excess of acetic acid, and more DCC/DMAP were added. TLC analysis again showed the presence of a new compound, eventually isolated in an overall yield of 74%, and shown to be the azide **38**. Reduction of this azide with propane-1,3-dithiol then gave the tethered primary amine **50**.

Try as we might, we could not convert the primary amine **50** into the secondary amine **51** using $Pd(PPh_3)_4$, in either the presence or absence of 1,5-bis(diphenylphosphino)pentane. The amine **50** seemed quite unreactive, with fragmentation of the ether linkage(s) a seemingly unwanted process.

In conclusion, we have been able to prepare several carbohydrate triflates, but only those that were not deoxygenated on the pyranose ring, namely **12** and **29**, were stable enough to alkylate our key cyclohexenyl amine **8** and so



Scheme 6. (*a*) 4-MeOC$_6$H$_4$CH$_2$OCH$_2$Cl, Mg, HgCl$_2$, THF, 0°C, then Ac$_2$O; (*b*) DDQ, CH$_2$Cl$_2$/H$_2$O; (*c*) Na, MeOH, 0°C; (*d*) **40**, DCC, DMAP, CH$_2$Cl$_2$, then HOAc, DCC, DMAP; (*e*) HS(CH$_2$)$_3$SH, Et$_3$N, MeOH.

form, ultimately, analogues of methyl β-acarviosin **4**. A related approach, involving the tethering of a cyclohexene ring to a pyranose amine, certainly generated a lot of new chemistry but was unsuccessful in the final intramolecular alkylation step.

Experimental

General experimental procedures have been given previously.[13]

*[(1*R*,4*R*,5*S*,6*S*)-4,5,6-Tribenzyloxy-3-(benzyloxymethyl)cyclohex-2-enyl]amine, Tetra*-O*-benzyl-1-epivalienamine **8***

[(1*R*,4*R*,5*S*,6*S*)-4,5,6-Tribenzyloxy-3-(benzyloxymethyl)cyclohex-2-enyl] azide[13] (3.3 g, 6.0 mmol), Na$_2$S · 9H$_2$O (2.75 g, 12.0 mmol), and Et$_3$N (200 μL) were heated in MeOH (50 mL) under reflux (3 h). Concentration of the mixture followed by a normal workup (CH$_2$Cl$_2$) and flash chromatography (toluene/EtOAc/EtOH/Et$_3$N, 60 : 35 : 4 : 1) gave the amine **8** as a waxy solid (2.4 g, 76%). The ^{1}H NMR (300 MHz) spectrum was consistent with that reported.[25]

Methyl 2,3,6-Tri-O*-benzoyl-4-deoxy-4-[(1′*R*,4′*R*,5′*S*,6′*S*)-4′,5′,6′-tribenzyloxy-3′-(benzyloxymethyl)cyclohex-2′-enyl]-amino-β-*D*-glucoside **13***

The amine **8** (780 mg, 1.5 mmol) and the triflate **12**[12] (465 mg, 0.73 mmol) in DMI (5 mL) were stirred at room temperature under nitrogen (4 days). Normal workup (Et$_2$O) gave a pale yellow oil that was purified by flash chromatography. First to elute (EtOAc/petrol, 3 : 17) was the alkene **14** as a colourless oil (96 mg, 27%), [α]$_D$ −87° (lit.[15] –86°). The ^{1}H NMR (300 MHz) spectrum was consistent with that reported.[12]

Next to elute (EtOH/toluene/EtOAc, 1 : 6 : 3) was the *amine* **13** as a colourless oil (305 mg, 41%) (Found C 74.0, H 6.0. C$_{63}$H$_{61}$NO$_{12}$ requires C 73.9, H 6.0%). δ_H (500 MHz) 3.15–3.23 (m, H4,7′), 3.27 (m, H1′), 3.36 (dd, $J_{1',6'}$ 8.5, $J_{5',6'}$ 9.5, H6′), 3.44 (s, OMe), 3.63 (ddd, $J_{4,5}$ 9.7, $J_{5,6}$ 5.3, 2.0, H5), 3.72 (dd, $J_{4',5'}$ 7.5, H5′), 3.76, 3.96 (ABq, *J* 11.7, C*H*$_2$Ph), 4.03 (br d, *J* 11.4, H7′), 4.12 (br d, H4′), 4.55, 4.68 (ABq, *J* 10.8, C*H*$_2$Ph), 4.60 (d, $J_{1,2}$ 7.5, H1), 4.66 (dd, $J_{6,6}$ 11.8, H6), 4.73, 4.89 (ABq, *J* 11.1, C*H*$_2$Ph), 4.84–4.95 (m, H6, C*H*$_2$Ph), 5.41–5.45 (m, H2, 3), 5.91 (br s, H2′), 7.15–7.61 (m, Ph). δ_C (125.8 MHz) 56.70 (OMe), 58.25 (C4), 60.13 (C1′), 63.21 (C6), 70.55 (C7′), 71.67 (*C*H$_2$Ph), 72.15, 74.88 (C2,3), 74.48, 75.00, 75.60 (3 C, *C*H$_2$Ph), 76.45 (C5), 79.14 (C4′), 82.96 (C6′), 84.24 (C5′), 101.52 (C1), 127.02 (C2′), 127.37–138.47 (C3′,Ph), 165.30, 165.98, 166.91 (3 C, C═O). *m*/*z* (FAB) 1024.4290 [(M + H)$^{+\bullet}$ requires 1024.4272].

Methyl 2,3,6-Tri-O*-acetyl-4-deoxy-4-[(1′*R*,4′*R*,5′*S*, 6′*S*)-4′,5′,6′-triacetoxy-3′-(acetoxymethyl)cyclohex-2′-enyl]amino-β-*D*-glucoside **15***

Sodium (5 mg) was added to the amine **13** (285 mg, 0.278 mmol) in MeOH (2 mL) and the mixture stirred at room temperature (3 h). The solution was concentrated, and then the residue taken up in dry THF (20 mL). NH$_3$ was added to the solution at −78°C until a precipitate was just seen. Small pieces of Li (20 mg, 2.8 mmol) were then added to the mixture with vigorous stirring, and the stirring continued at −78°C (1 h). NH$_4$OAc (77 mg, 1.0 mmol) was added to the mixture and the solvents were removed by evaporation. The resulting residue was treated with Ac$_2$O (2 mL), pyridine (1 mL), and DMAP (20 mg) and the mixture left to stir overnight. Normal workup (CH$_2$Cl$_2$) followed by flash chromatography (EtOAc/petrol, 1 : 1) gave the heptaacetate **15** as a colourless oil (133 mg, 74%), [α]$_D$ −65° (lit.[10] −68°). Spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those reported.[10]

*Methyl 4-Deoxy-4-[(1′*R*,4′*R*,5′*S*,6′*S*)-4′,5′,6′-trihydroxy-3′-(hydroxymethyl)cyclohex-2′-enyl]amino-β-*D*-glucoside **10***

Sodium (5 mg) was added to the heptaacetate **15** (200 mg) in MeOH (5 mL) and the mixture stirred at room temperature (1 h). The solution was then neutralized (Amberlite IR-120, H$^+$) and concentrated to give the polyol **10** as a colourless glass (102 mg), [α]$_D$ −75° (H$_2$O; lit.[10] −75°). Spectroscopic data (^{1}H and ^{13}C NMR) were consistent with those reported.[10]

Methyl 2,6-Di-O*-benzyl-3,4*-O*-thiocarbonyl-β-*D*-galactoside **19***

A solution of the diol **17**[24] (610 mg, 1.63 mmol) and Bu$_2$SnO (850 mg, 3.42 mmol) in toluene (100 mL) was distilled over 3 h to a final volume of approximately 20 mL. The solution was then cooled to 0°C and *O*-phenyl chlorothioformate (280 μL, 2.12 mmol) was added dropwise with stirring. The solution was allowed to warm to room temperature and stirring continued (2 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 3 : 7) of the residue gave the *thiocarbonate* **19** as a colourless oil (510 mg, 75%), [α]$_D$ −26° (Found

C 63.6, H 5.9. $C_{22}H_{24}O_6S$ requires C 63.4, H 5.8%). δ_H (300 MHz) 3.48 (s, OMe), 3.63 (dd, $J_{1,2}$ 5.4, $J_{2,3}$ 4.3, H2), 3.78 (2 H, br d, $J_{5,6}$ 6.6, H6), 4.08 (dt, $J_{4,5}$ 1.8, H5), 4.56 (d, H1), 4.57, 4.91 (ABq, J 12.0, CH_2Ph), 4.68, 4.77 (ABq, J 11.8, CH_2Ph), 4.92 (dd, $J_{3,4}$ 8.0, H3), 4.99 (dd, H4), 7.29–7.40 (10 H, m, Ph). δ_C (75.5 MHz) 56.13 (OMe), 68.06 (C6), 69.38, 75.73 (C2,5), 73.46, 73.58 (2 C, CH$_2$Ph), 78.60, 80.25 (C3,4), 100.73 (C1), 127.63–137.29 (Ph), 190.79 (C═S).[26] m/z (FAB) 417.1349 [(M + H)$^{+\bullet}$ requires 417.1372].

*Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-β-D-galactoside* ***20***

Trifluoroacetic acid (1 drop) was added to the diol **17** (1.00 g) and $CH_3C(OEt)_3$ (1 mL) in $CHCl_3$ (10 mL), and the solution stirred at room temperature (5 min). MeCN (10 mL) and H_2O (1 mL) were then added and the mixture stirred vigorously (30 min). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 3 : 7) of the residue gave the acetate **20** as a colourless oil (1.06 g, 95%), $[\alpha]_D$ −9.0° (lit.[27] −9.5°). The ^{1}H NMR spectrum was consistent with that reported.[27] δ_C (75.5 MHz) 20.77 (Me), 56.50 (OMe), 67.98, 68.25, 72.79, 72.83, 73.32, 74.88 (7 C, C2, 3, 4, 5, 6, CH$_2$Ph), 106.07 (C1), 127.39–137.72 (Ph), 170.03 (C═O).

*Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-3-*O*-phenoxythiocarbonyl-β-D-galactoside*

O-Phenyl chlorothioformate (0.32 mL, 2.0 mmol) was added to the acetate **20** (0.51 g, 1.2 mmol) and pyridine (0.3 mL) in CH_2Cl_2 (30 mL) at room temperature and the mixture stirred (4 h). Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 3 : 17) gave the title *thiocarbonate* as a colourless oil (465 mg, 70%), $[\alpha]_D$ +29° (Found C 65.2, H 5.7. $C_{30}H_{32}O_8S$ requires C 65.3, H 5.8%). δ_H (300 MHz) 3.54 (dd, $J_{5,6}$ 6.7, $J_{6,6}$ 9.6, H6), 3.61 (dd, $J_{5,6}$ 6.7, H6), 3.62 (s, OMe), 3.81 (dd, $J_{1,2}$ 7.5, $J_{2,3}$ 9.9, H2), 3.89 (br t, H5), 4.47 (d, H1), 4.43, 4.59 (ABq, J 12.0, CH_2Ph), 4.70, 4.93 (ABq, J 11.5, CH_2Ph), 5.55 (dd, $J_{3,4}$ 3.5, H3), 5.74 (dd, $J_{4,5}$ 0.9, H4), 7.09–7.45 (15 H, m, Ph). δ_C (75.5 MHz) 20.67 (Me), 57.39 (OMe), 66.95, 71.81, 77.09, 81.91 (C2, 3, 4, 5), 67.74, 73.63, 74.94 (3 C, C6, CH$_2$Ph), 104.48 (C1), 121.87–138.26 (Ph), 153.49 (C═S),[26] 169.95 (C═O). m/z (FAB) 553.1896 [(M + H)$^{+\bullet}$ requires 553.1899].

*Methyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-3-deoxy-β-D-*xylo*-hexoside* ***21***

Tributyltin hydride (0.53 ml, 1.9 mmol) was added to the above thiocarbonate (430 mg, 0.78 mmol) and azobisisobutyronitrile (AIBN; 20 mg) in toluene (30 mL), and the mixture stirred at 70°C (5 h). Concentration of the mixture followed by normal workup (EtOAc) and flash chromatography (EtOAc/petrol, 3 : 17) gave the D-*xylo*-hexoside **21** as a colourless oil (220 mg, 71%), $[\alpha]_D$ +64° (Found C 68.8, H 7.0. $C_{23}H_{28}O_6$ requires C 69.0, H 7.1%). δ_H (300 MHz) 1.70 (ddd, $J_{2,3}$ 11.8, $J_{3,3}$ 14.6, $J_{3,4}$ 3.1, H3), 1.93 (s, Me), 2.33 (ddd, $J_{2,3}$ 3.1, $J_{3,4}$ 5.1, H3), 3.48–3.60 (3 H, m, H2,6), 3.59 (s, OMe), 3.81 (dt, $J_{4,5}$ 1.3, $J_{5,6} \approx J_{5,6}$ 6.1, H5), 4.37 (d, $J_{1,2}$ 7.6, H1), 4.45, 4.58 (ABq, J 12.0, CH_2Ph), 4.67, 4.95 (ABq, J 11.7, CH_2Ph), 5.11 (m, H4), 7.24–7.49 (10 H, m, Ph). δ_C (75.5 MHz) 20.76 (Me), 33.67 (C3), 56.48 (OMe), 67.98, 72.83, 74.88 (C2,4,5), 68.25 (C6), 72.79, 73.32 (2 C, CH$_2$Ph), 106.07 (C1), 127.38–137.72 (Ph), 170.03 (C═O). m/z (FAB) 399.1832 [(M − H)$^{+\bullet}$ requires 399.1808].

*Methyl 2,6-Di-*O*-benzyl-3-deoxy-β-D-*xylo*-hexopyranoside* ***22***

Sodium (4 mg) was added to the acetate **21** (160 mg) in dry MeOH (8 mL) and the mixture stirred (1 h). The solution was neutralized (Amberlite IR-120, H$^+$), and then concentrated. Flash chromatography (EtOAc/petrol, 1 : 3) of the residue gave the alcohol **22** as a colourless solid (135 mg, 94%), $[\alpha]_D$ +26° (lit.[28] +25°). δ_H (300 MHz) 1.54 (ddd, $J_{2,3}$ 11.6, $J_{3,3}$ 14.5, $J_{3,4}$ 3.0, H3), 2.22 (ddd, $J_{2,3}$ 3.2, $J_{3,4}$ 5.2, H3), 2.73 (br s, OH), 3.51 (s, OMe), 3.53–3.70 (4 H, m, H2, 5, 6), 3.90 (m, H4), 4.26 (d, $J_{1,2}$ 7.6, H1), 4.49, 4.53 (ABq, J 11.9, CH_2Ph), 4.56, 4.76 (ABq, J 11.7, CH_2Ph), 7.05–7.28 (10 H, m, Ph). δ_C (75.5 MHz) 36.46 (C3), 56.40 (OMe), 67.01, 72.90, 75.79 (C2, 4, 5), 69.86, 72.83, 73.56 (3 C, C6,CH$_2$Ph), 106.50 (C1), 122.49–138.57 (Ph).

*Methyl 2,6-Di-*O*-benzyl-3-deoxy-4-*O*-methanesulfonyl-β-D-*xylo*-hexoside* ***23***

Methanesulfonyl chloride (72 μL, 0.94 mmol) was added to the alcohol **22** (280 mg, 0.78 mmol) and pyridine (76 μL, 0.94 mmol) in CH_2Cl_2 (10 mL) at 0°C. The mixture was then stirred at room temperature (1 h). Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 1 : 3) gave the *mesylate* **23** as a colourless oil (310 mg, 91%), $[\alpha]_D$ −41° (Found C 60.5, H 6.5. $C_{16}H_{22}O_5$ requires C 60.5, H 6.5%). δ_H (300 MHz) 1.75 (ddd, $J_{2,3}$ 11.7, $J_{3,3}$ 14.5, $J_{3,4}$ 2.6, H3), 2.22 (ddd, $J_{2,3}$ 3.2, $J_{3,4}$ 5.1, H3), 2.88 (s, Me), 3.55–3.67 (3 H, m, H2,6), 3.64 (s, OMe), 3.79 (ddd, $J_{4,5}$ 1.0, $J_{5,6} \approx J_{5,6}$ 6.8, H5), 4.35 (d, $J_{1,2}$ 7.8, H1), 4.52, 4.57 (ABq, J 11.7, CH_2Ph), 4.62, 4.83 (ABq, J 11.7, CH_2Ph), 4.94 (m, H4), 7.21–7.49 (10 H, m, Ph). δ_C (75.5 MHz) 34.70 (C3), 52.37 (Me), 56.60 (OMe), 67.84 (C6), 72.07, 74.49, 75.02 (C2,4,5), 73.01, 73.52 (2 C, CH$_2$Ph), 105.98 (C1), 125.65–138.20 (Ph).

*Methyl 4-*O*-Acetyl-2-*O*-benzyl-6-deoxy-β-D-galactoside*

Trifluoroacetic acid (1 drop) was added to the diol **26**[9] (1.10 g) and $CH_3C(OEt)_3$ (4 mL) in $CHCl_3$ (15 mL) at room temperature and the solution stirred (2 min). MeCN (40 mL) and H_2O (1 mL) were then added and the mixture was stirred vigorously (20 min). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 1 : 1) of the residue gave the title *alcohol* as a colourless oil (1.05 g, 83%), $[\alpha]_D$ +21° (Found C 61.9, H 7.1. $C_{16}H_{22}O_6$ requires C 61.9, H 7.2%). δ_H (300 MHz) 1.21 (3 H, d, $J_{5,6}$ 6.5, H6), 1.95 (s, Me), 3.48 (dd, $J_{1,2}$ 7.7, $J_{2,3}$ 9.7, H2), 3.58 (s, OMe), 3.69 (dq, $J_{4,5}$ 1.1, H5), 3.76 (dd, $J_{3,4}$ 3.6, H3), 4.29 (d, H1), 4.64, 4.97 (ABq, J 11.3, CH_2Ph), 5.17 (dd, H4), 7.13–7.39 (m, Ph). δ_C (75.5 MHz) 16.21 (C6), 20.77 (Me), 50.02 (OMe), 69.17, 71.83, 72.11, 79.08 (C2, 3, 4, 5), 74.63 (CH$_2$Ph), 104.54 (C1), 125.24–138.30 (Ph), 171.26 (C═O). m/z (FAB) 311.1483 [(M + H)$^{+\bullet}$ requires 311.1495].

*Methyl 4-*O*-Acetyl-2-*O*-benzyl-6-deoxy-3-*O*-phenoxythiocarbonyl-β-D-galactoside*

O-Phenyl chlorothioformate (1.1 mL, 7.0 mmol) was added to the above alcohol (1.46 g, 4.70 mmol) and pyridine (1 mL) in dry CH_2Cl_2 (30 mL) at room temperature, and the mixture stirred (6 h). Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 3 : 17) gave the title *thiocarbonate* as colourless needles (1.60 g, 76%), mp 85–86°C (Et_2O), $[\alpha]_D$ +39° (Found C 61.8, H 5.9. $C_{23}H_{26}O_7S$ requires C 61.9, H 5.9%). δ_H (300 MHz) 1.22 (3 H, d, $J_{5,6}$ 6.5 Hz, H6), 2.01 (s, Me), 3.59 (s, OMe), 3.81 (dd, $J_{1,2}$ 7.5, $J_{2,3}$ 9.9, H2), 3.89 (br t, H5), 4.47 (d, H1), 4.63, 4.82 (ABq, J 12.0, CH_2Ph), 5.54 (dd, $J_{3,4}$ 3.4, H3), 5.74 (d, H4), 7.09–7.45 (10 H, m, Ph). δ_C (75.5 MHz) 16.76 (C6), 21.32 (Me), 57.01 (OMe), 67.56, 72.64, 77.45, 81.89 (C2, 3, 4, 5), 73.56 (CH$_2$Ph), 105.43 (C1), 121.70–139.80 (Ph), 152.99 (C═S),[26] 169.90 (C═O). m/z (FAB) 447.1450 [(M + H)$^{+\bullet}$ requires 447.1478].

*Methyl 4-*O*-Acetyl-2-O-benzyl-3,6-dideoxy-β-D-*xylo*-hexoside*

Tributyltin hydride (1.65 mL, 6.10 mmol) was added to the above thiocarbonate (2.10 g, 4.70 mmol) and AIBN (30 mg) in toluene (30 mL), and the mixture stirred at 70°C (5 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 3 : 17) of the residue gave the title D-*xylo*-hexoside as colourless plates (1.13 g, 82%), mp 63–65°C (Pr^i_2O/EtOAc), $[\alpha]_D$ −32° (Found C 65.3, H 7.7. $C_{16}H_{22}O_5$ requires C 65.3, H 7.5%). δ_H (300 MHz) 1.22 (3 H, d, $J_{5,6}$ 6.5, H6), 1.73 (ddd, $J_{2,3}$ 11.7, $J_{3,3}$ 14.6, $J_{3,4}$ 3.1, H3), 2.10 (s, Me), 2.28 (ddd, $J_{2,3}$ 5.1, $J_{3,4}$ 3.1, H3), 3.54 (ddd, $J_{1,2}$ 7.6, H2), 3.59 (s, OMe), 3.73 (dq, $J_{4,5}$ 1.4, H5), 4.34 (d, H1), 4.63, 4.87 (ABq, J 11.8, CH_2Ph), 4.94 (ddd, H4), 7.27–7.48 (m, Ph). δ_C (75.5 MHz) 16.22 (C6), 20.75 (Me), 33.99 (C3), 56.30 (OMe), 70.39, 71.74, 72.75 (C2, 4, 5), 72.65 (CH$_2$Ph), 105.91 (C1), 127.31–138.38 (Ph), 170.35 (C═O). m/z (FAB) 293.1387 [(M + H)$^{+\bullet}$ requires 293.1389].

*Methyl 2-*O*-Benzyl-3,6-dideoxy-β-D-*xylo*-hexopyranoside* ***27***

Sodium (5 mg) was added to the above D-*xylo*-hexoside (157 mg) in dry MeOH (10 mL) and the mixture stirred (1 h). The solution was

neutralized (Amberlite IR-120, H^+), and then concentrated. Flash chromatography (EtOAc/petrol, 1 : 3) of the residue gave the alcohol **27** as colourless needles (131 mg, 97%), mp 85°C (Pr^i_2O/EtOAc; lit.[28] 84–85°C), $[\alpha]_D$ –24° (lit.[28] –23°). δ_H (200 MHz) 1.36 (3 H, d, $J_{5,6}$ 10.5, H6), 1.63 (ddd, $J_{2,3}$ 11.1, $J_{3,3}$ 14.2, $J_{3,4}$ 3.2, H3), 1.95 (br s, OH), 2.31 (ddd, $J_{2,3}$ 5.2, $J_{3,4}$ 3.1, H3), 3.52 (ddd, $J_{1,2}$ 7.9, H2), 3.57 (OMe), 3.61–3.72 (m, H4, 5), 4.29 (d, H1), 4.61, 4.81 (ABq, J 11.7, CH_2Ph), 7.29–7.37 (m, Ph).

*Attempted Coupling of the Triflate **24** and the 1-Epivalienamine Derivative **8***

Trifluoromethanesulfonic anhydride (140 μL, 0.82 mmol) was added to the alcohol **27** (170 mg, 0.68 mmol) and pyridine (70 μL, 0.85 mmol) in CH_2Cl_2 (10 mL) at −15°C. The mixture was stirred (20 min) at this temperature until TLC analysis showed complete conversion of the starting material into a less polar product, presumed to be the triflate **24**. The solution was then diluted with DMI (5 mL) and the CH_2Cl_2 removed under vacuum, without heating, to give a colourless solution. The 1-epivalienamine derivative **8** (720 mg, 1.35 mmol) was added to this solution and the mixture kept at room temperature (4 days). Normal workup (Et_2O) and flash chromatography (EtOAc/petrol, 3 : 17) gave a colourless oil (140 mg) that appeared to be a mixture of alkenes (by ^1H and ^{13}C NMR spectroscopy).

*Methyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-β-D-alloside **33***

(*a*) Diethyl azodicarboxylate (630 μL, 4.00 mmol) was added to the alcohol **31**[16] (780 mg, 2.0 mmol), Ph_3P (1.0 g, 4.0 mmol), and $ClCH_2COOH$ (280 mg, 3.0 mmol) in C_6H_6 (50 mL) and THF (10 mL) at 0°C. The solution was then stirred at room temperature (7 h). The solution was concentrated and the residue subjected to flash chromatography (EtOAc/petrol, 3 : 20 to 1 : 2) to give the chloroacetate **32** as an oil that was carried through to the next step. δ_H (300 MHz) 3.56 (s, Me), 3.80–3.90 (m, H4,6), 4.02–4.08 (m, H5), 4.11, 4.17 (ABq, J 14.4, CH_2Cl), 4.45 (dd, $J_{5,6}$ 5.1, $J_{6,6}$ 10.5, H6), 4.92 (d, $J_{1,2}$ 8.2, H1), 5.18 (dd, $J_{2,3}$ 3.1, H2), 5.59 (s, CHPh), 5.98 (br t, $J_{3,4}$ 3.1, H3), 7.38–8.03 (10 H, m, Ph).

(*b*) The chloroacetate **32** was treated with thiourea (1.5 g, 20 mmol) and 2,6-lutidine (230 μL, 2.0 mmol) in CH_2Cl_2/MeOH (40 mL, 1 : 1) at reflux (12 h). Concentration of the mixture followed by flash chromatography (EtOAc/petrol, 3 : 20 to 1 : 3) of the residue gave the *alcohol* **33** (640 mg, 83% from **31**) as fine needles, mp 177–178°C (Pr^i_2O), $[\alpha]_D$ −58° (Found C 65.4, H 5.9. $C_{22}H_{22}O_7$ requires C 65.3, H 5.7%). δ_H (300 MHz) 3.54 (s, Me), 3.73 (dd, $J_{3,4}$ 2.4, $J_{4,5}$ 9.4, H4), 3.82 (dd, $J_{5,6} \approx J_{6,6}$ 10.3, H6), 4.05–4.18 (m, H5), 4.44 (dd, $J_{5,6}$ 5.0, H6), 5.57–5.63 (m, H3), 5.01 (m, H1, 2), 5.61 (s, CHPh), 7.37–8.15 (10 H, m, Ph). δ_C (75.5 MHz) 57.38 (Me), 63.19, 67.96, 72.23, 78.41 (C2, 3, 4, 5), 69.06 (C6), 100.03, 101.79 (C1, *C*HPh), 126.14–136.90 (Ph), 165.39 (C═O).

*Methyl 2,4-Di-*O*-benzoyl-6-bromo-6-deoxy-β-D-alloside **34***

A mixture of the alcohol **33** (290 mg, 0.75 mmol), NBS (150 mg, 0.82 mmol) and $CaCO_3$ (80 mg, 0.82 mmol) in CCl_4 (10 mL) was heated under reflux (3 h), during which time the mixture changed from red to yellow. The mixture was concentrated and subjected to a normal workup (CH_2Cl_2) to give a residue that was purified by flash chromatography (EtOAc/petrol, 1 : 4) to yield the *bromide* **34** (350 mg, 77%) as cubes, mp 140–141°C (Pr^i_2O/petrol), $[\alpha]_D$ −14° (Found C 54.3, H 4.4. $C_{22}H_{21}BrO_7$ requires C 54.2, H, 4.6%). δ_H (300 MHz) 3.52 (dd, $J_{5,6}$ 7.0, $J_{6,6}$ 11.2, H6), 3.57 (s, Me), 3.61 (dd, $J_{5,6}$ 2.8, H6), 4.37–4.44 (m, H5), 4.67–4.68 (m, H3), 5.03 (d, $J_{1,2}$ 7.8, H1), 5.07 (dd, $J_{2,3}$ 2.8, H2), 5.10 (dd, $J_{3,4}$ 2.7, $J_{4,5}$ 9.1, H4), 7.38–8.09 (10 H, m, Ph). δ_C (75.5 MHz) 32.03 (C6), 56.94 (Me), 67.68, 70.90, 71.58, 71.85 (C2, 3, 4, 5), 99.29 (C1), 128.38–133.64 (Ph), 165.04, 165.14 (2 C, C═O).

*Methyl 2,4-Di-*O*-benzoyl-6-deoxy-β-D-alloside **35***

The bromide **34** (590 mg, 1.3 mmol) was treated with Bu_3SnH (0.42 mL, 2.1 mmol) in toluene (7 mL, 70°C, 3 h). The solution was concentrated and the residue was partitioned between MeCN and petrol. Concentration of the MeCN extract gave an oil that was purified by flash chromatography (EtOAc/petrol, 3 : 20 to 1 : 3) to give the *alcohol* **35** as a glass (420 mg, 81%), $[\alpha]_D$ −11° (Found C 65.3, H 5.9. $C_{22}H_{22}O_7$ requires C 65.3, H 5.7%). δ_H (300 MHz) 1.33 (3 H, d, $J_{5,6}$ 6.3, H6), 3.56 (s, OMe), 4.23–4.34 (m, H5), 4.65 (m, H3), 4.94 (dd, $J_{3,4}$ 2.7, $J_{4,5}$ 9.7, H4), 4.99 (d, $J_{1,2}$ 8.1, H1), 5.09 (dd, $J_{2,3}$ 2.9, H2), 7.71–8.13 (10 H, m, Ph). δ_C (75.5 MHz) 17.60 (C6), 56.88 (OMe), 67.52, 68.02, 72.16, 74.16 (C2, 3, 4, 5), 99.16 (C1), 128.42–133.46 (Ph), 165.15, 165.27 (2 C, C═O).

*Methyl 2,4-Di-*O*-benzoyl-6-deoxy-3-O-trifluoromethanesulfonyl-β-D-alloside **29***

Trifluoromethanesulfonic anhydride (190 μL, 1.6 mmol) was added to the alcohol **35** (390 mg, 0.98 mmol) and pyridine (150 μL, 2.2 mmol) in CH_2Cl_2 (5 mL) at −20°C. The mixture was allowed to warm to room temperature (2 h) and was then quenched with saturated $NaHCO_3$ solution (5 mL). Normal workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 3 : 20 to 1 : 4) gave the triflate **29** as a glass (440 mg, 86%), $[\alpha]_D$ −2.5°. δ_H (300 MHz) 1.38 (3 H, d, $J_{5,6}$ 6.2, H6), 3.57 (s, OMe), 4.18–4.30 (m, H5), 4.92 (d, $J_{1,2}$ 8.2, H1), 5.10 (dd, $J_{3,4}$ 2.3, $J_{4,5}$ 9.9, H4), 5.28 (dd, $J_{2,3}$ 2.3, H2), 5.64 (m, H3), 7.38–8.12 (10 H, m, Ph). δ_C (75.5 MHz) 17.38 (Me), 57.1 (OMe), 67.92, 69.18, 71.02 (C2, 4, 5), 84.52 (C3), 98.90 (C1), 118.19 (q, $J_{C,F}$ 319, CF_3), 128.20–138.83 (Ph), 164.87, 164.99 (2 C, C═O). m/z (FAB) 519.0951 [$(M + H)^{+\bullet}$ requires 519.0937].

*Methyl 2,4-Di-*O*-benzoyl-3,6-dideoxy-3-[(1′R,4′R,5′S, 6′S)-4′,5′,6′-tribenzyloxy-3′-(benzyloxymethyl)cyclohex-2′-enyl]amino-β-D-glucoside **36***

The triflate **29** (280 mg, 0.50 mmol) and the amine **8** (650 mg, 1.25 mmol) in DMI (1.5 mL) were stirred overnight. Normal workup (Et_2O) followed by flash chromatography (EtOAc/petrol/Et_3N, 15 : 84 : 1 to 25 : 74 : 1) gave the *amine* **36** as a glass (250 mg, 55%), $[\alpha]_D$ −67° (Found C 74.3, H 6.2. $C_{56}H_{57}NO_{10}$ requires C 74.4, H 6.4%). δ_H (500 MHz) 1.32 (3 H, d, $J_{5,6}$ 6.2, H6), 3.17–3.28 (m, H1′), 3.32–3.37 (m, H3), 3.42–3.56 (m, H6′,7′), 3.47 (s, OMe), 3.72–3.89 (m, H5), 3.92–4.03 (m, H5′), 4.07 (d, $J_{7',7'}$ 11.7, H7′), 4.16 (br d, $J_{4',5'}$ 11.6, H4′), 4.36–4.65 (9 H, m, H1, CH_2Ph), 4.86–4.97 (m, H4), 5.10–5.25 (m, H2), 5.57 (br s, H2′), 6.95–8.02 (m, Ph). δ_C (125.8 MHz) 17.89 (C6), 56.61 (OMe), 58.46, 59.87, 71.16, 74.93, 76.46, 78.90, 81.88, 83.74 (C2, 3, 4, 5, 1′, 4′, 5′, 6′), 70.51, 71.72, 74.18, 74.38 (4 C, C7′, *C*H$_2$Ph), 102.29 (C1), 127.44–138.34 (C2′,3′, Ph), 165.27, 165.63 (2 C, C═O); the signal for either C7′ or a *C*H$_2$Ph could not be located.

*Methyl 2,4-Di-*O*-acetyl-3,6-dideoxy-3-[(1′R,4′R,5′S,6′S)-4′,5′,6′-triacetoxy-3′-(acetoxymethyl)cyclohex-2′-enyl]amino-β-D-glucoside **37***

A small piece of Na was added to the amine **36** (95 mg) in MeOH (10 mL). The mixture was stirred overnight, after which time it was concentrated. Small pieces of Na were added to a solution of the residue in THF (10 mL) and NH_3 (30 mL) at −78°C until the solution remained blue for 1 h. NH_4Cl was added so as to dissipate this colour. Evaporation of the solvents gave an off-white residue that was treated with Ac_2O/pyridine (6 mL, 1 : 2) for 5 h. Normal workup (CH_2Cl_2) followed by flash chromatography (EtOAc/petrol, 4 : 6) gave the *hexaacetate* **37** as needles (37 mg, 59%), mp 158°C (Pr^i_2O/EtOH), $[\alpha]_D$ −67° (Found C 52.9, H 6.6. $H_{26}H_{37}NO_{14}$ requires C 53.1, H 6.4%). δ_H (300 MHz) 1.20 (3 H, d, $J_{5,6}$ 6.2, H6), 1.98, 2.02, 2.04, 2.08, 2.10 (18 H, 5 s, Ac), 2.88 (dd, $J_{2,3} \approx J_{3,4}$ 10.0, H3), 3.43 (s, OMe), 3.43–3.58 (m, H5,1′), 4.26 (d, $J_{1,2}$ 7.9, H1), 4.36 (d, $J_{7',7'}$ 12.8, H7′), 4.56 (dd, $J_{4,5}$ 9.7, H4), 4.62 (br s, H7′), 4.74 (dd, H2), 4.91 (dd, $J_{1',6'}$ 8.9, $J_{5',6'}$ 10.7, H6′), 5.19 (dd, $J_{4',5'}$ 7.7, H5′), 5.68 (br s, H4′), 5.72 (br s, H2′). δ_C (75.5 MHz) 17.55 (C6), 20.63, 20.67, 20.71, 20.89, 20.97 (6 C, CO*Me*), 56.42, 57.45, 59.98, 70.63, 71.21, 72.85, 74.06, 75.80 (C2, 3, 4, 5, 1′, 4′, 5′, 6′), 62.93 (C7′), 101.83 (C1), 120.24 (C2′), 130.66 (C3′), 169.98, 170.21, 170.32, 170.37 (6 C, C═O).

*Methyl 3,6-Dideoxy-3-[(1′*R*,4′*R*,5′*S*,6′*S*)-4′,5′,6′-trihydroxy-3′-(hydroxymethyl)cyclohex-2′-enyl]amino-β-*D*-glucoside **7***

A small piece of Na was added to the hexaacetate **37** (120 mg) in MeOH (5 mL) at 0°C. The mixture was stirred at room temperature (1 h), and then neutralized (Dowex 50W-X8, H^+), filtered, and the filtrate concentrated to give a yellow oil. This oil was filtered through a Sephadex plug (A-25, MeOH) to give, after evaporation, the polyol **7** as a colourless oil (57 mg), $[\alpha]_D$ −92° (MeOH). δ_H (600 MHz) 1.29 (d, $J_{5,6}$ 6.2, H6), 3.16–3.24 (m, H3,4), 3.38–3.44 (m, H5), 3.46 (dd, $J_{1,2}$ 7.6, $J_{2,3}$ 9.3, H2), 3.53 (s, OMe), 3.58 (dd, $J_{4',5'}$ 7.1, $J_{5',6'}$ 9.3, H5′), 3.72 (dd, $J_{5',6'}$ 8.1, H6′), 4.07–4.14 (m, H1′,4′), 4.18 (2 H, br s, H7′), 4.24 (d, H1), 5.87 (br s, H2′). δ_C (150 MHz) 17.86 (C6), 57.37, 61.51, 64.64, 72.71, 73.25, 73.40, 74.25, 76.96 (C2, 3, 4, 5, 1′, 4′, 5′, 6′), 105.42 (C1), 118.35 (C2′), 144.59 (C3′). *m*/*z* (FAB) 336.1675 [$(M + H)^{+\bullet}$ requires 336.1658].

*Methyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-β-*D*-galactoside*

Methyl β-D-galactopyranoside (7.2 g, 37 mmol) in DMF (50 mL) was treated with benzaldehyde dimethyl acetal (7.6 g, 50 mmol) and CSA (500 mg) under reduced pressure (60°C, 2 h). Triethylamine (1 mL) was added to the solution, which was then concentrated to half its volume. This solution was diluted with more DMF (50 mL), and NaH (4.4 g, 60% dispersion in mineral oil, 110 mmol) and BnBr (11.4 mL, 96 mmol) were then added. The mixture was stirred (1 h) and then MeOH (2 mL) was cautiously added. Concentration of the mixture followed by a normal workup (CH_2Cl_2) gave an orange oil. This oil was purified by rapid silica filtration (RSF) (EtOAc/petrol, 1 : 10 to 1 : 3) to give the title dibenzyl ether as colourless crystals (11.6 g, 68%), mp 112°C (Et_2O/petrol; lit.[29] 116.8°).

*Methyl 2,3-Di-*O*-benzyl-6-*O*-(t-butyldimethylsilyl)-β-*D*-galactopyranoside **42***

The above dibenzyl ether (5.6 g, 12 mmol) was treated with aqueous AcOH (70 mL of 80%; 100°C, 30 min). Concentration of the mixture followed by RSF (EtOAc/petrol, 1 : 1 to EtOAc) then gave what was presumed to be methyl 2,3-di-*O*-benzyl-β-D-galactopyranoside **41** as a colourless oil. This oil was treated with *t*-butyldimethylsilyl chloride (2.08 g, 13.3 mmol) and imidazole (1.03 g, 15.1 mmol) in DMF (20 mL) for 1 day. MeOH (1 mL) was added and the mixture was stirred (20 min). Concentration of the mixture followed by normal workup (CH_2Cl_2) and flash chromatography (EtOAc/petrol, 1 : 9 to 1 : 4) gave the *silyl ether* **42** as an oil (4.46 g, 75%), $[\alpha]_D$ −28° (Found C 67.2, H 8.3. $C_{28}H_{40}O_6Si$ requires C 67.2, H 8.0%). δ_H (300 MHz) 0.11 (s, $SiMe_2$), 0.92 (s, CMe_3), 3.38 (m, H5), 3.48 (dd, $J_{2,3}$ 3.3, $J_{3,4}$ 9.4, H3), 3.55 (s, OMe), 3.64 (dd, $J_{1,2}$ 7.7, H2), 3.82 (dd, $J_{5,6}$ 5.5, $J_{6,6}$ 10.2, H6), 3.90 (dd, $J_{5,6}$ 6.4, H6), 3.99 (m, H4), 4.28 (d, H1), 4.71–4.93 (4 H, m, CH_2Ph), 7.22–7.48 (10 H, m, Ph). δ_C (75.5 MHz) −5.46 ($SiMe_2$), 18.24 (*C*Me_3), 25.81 (C*Me*$_3$), 56.74 (OMe), 62.18 (C6), 66.44, 74.25, 79.06, 80.68 (C2, 3, 4, 5), 72.35, 75.03 (2 C, *C*H_2Ph), 104.68 (C1), 127.48–138.70 (Ph).

*Methyl 4-Azido-2,3-di-*O*-benzyl-6-*O*-(t-butyldimethylsilyl)-4-deoxy-β-*D*-glucoside **44***

Trifluoromethanesulfonic anhydride (0.82 mL, 5.8 mmol) was added to the silyl ether **42** (1.9 g, 3.9 mmol) and pyridine (1.0 mL) in CH_2Cl_2 (20 mL), and the mixture stirred (2 h, 0°C). The addition of saturated $NaHCO_3$ solution followed by a normal workup (CH_2Cl_2) gave, presumably, methyl 2,3-di-*O*-benzyl-6-*O*-(*t*-butyldimethylsilyl)-4-*O*-(trifluoromethanesulfonyl)-β-D-galactoside **43** as a yellow oil. This oil was treated with NaN_3 (0.65 g, 12 mmol) in DMF (1 h, 80°). Concentration of the mixture and normal workup (CH_2Cl_2) gave an oil that was subjected to flash chromatography (EtOAc/petrol, 1 : 9) to give the *azide* **44** as an oil (1.93 g, 93%), $[\alpha]_D$ +87° (Found C 64.2, H 7.6, N 7.9. $C_{28}H_{39}N_3O_5$ requires C 64.0, H 7.5, N 8.0%). δ_H (300 MHz) 0.10 (s, $SiMe_2$), 0.92 (s, CMe_3), 3.12–3.16 (m, $J_{4,5}$ 9.5, H5), 3.40 (dd, $J_{1,2} \approx J_{2,3}$ 7.9, H2), 3.46–3.62 (m, H3,4), 3.54 (s, OMe), 3.84 (dd, $J_{5,6}$ 3.9, $J_{6,6}$ 11.5, H6), 3.98 (dd, $J_{5,6}$ 2.0, H6), 4.27 (d, H1), 4.70–5.05 (4 H, m, CH_2Ph), 7.28–7.43 (10 H, m, Ph). δ_C (75.5 MHz) −5.23, −5.46 ($SiMe_2$), 18.35 (*C*Me_3), 25.87 (C*Me*$_3$), 56.48 (OMe), 61.62 (C4), 62.66 (C6), 74.77, 75.71 (2 C, *C*H_2Ph), 74.88, 77.42, 82.24 (C2, 3, 4, 5), 104.52 (C1), 104.52–138.40 (Ph).

*Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-β-*D*-glucoside **45***

The silyl ether **44** (1.93 g) was treated with aqueous AcOH (20 mL of 80%, 100°C, 30 min). Concentration of the mixture gave an oil that was subjected to flash chromatography (EtOAc/petrol, 2 : 3) to give the *alcohol* **45** as needles (1.38 g, 91%), mp 92–93°C (Pr^i_2O), $[\alpha]_D$ +128° (Found C 63.6, H 6.2, N 10.3. $C_{21}H_{25}N_3O_5$ requires C 63.2, H 6.3, N 10.5%). δ_H (300 MHz) 3.11–3.18 (m, H5), 3.32–3.50 (m, H2,3,4), 3.52 (s, Me), 3.70 (dd, $J_{5,6}$ 4.5, $J_{6,6}$ 12.1, H6), 3.84 (dd, $J_{5,6}$ 2.6, H6), 4.28 (d, $J_{1,2}$ 7.2, H1), 4.61–4.90 (4 H, m, CH_2Ph), 7.14–7.48 (10 H, m, Ph). δ_C (75.5 MHz) 57.30 (Me), 61.31, 74.19, 82.09, 82.68 (C2, 3, 4, 5), 62.12 (C6), 74.80, 75.57 (2 C, *C*H_2Ph), 104.74 (C1), 127.76–138.16 (Ph).

*Methyl 4-Azido-2,3-di-*O*-benzyl-6-*O*-(2-carboxybenzoyl)-4-deoxy-β-*D*-glucoside **40***

The alcohol **45** (0.94 g, 2.4 mmol) was treated with phthalic anhydride (1.73 g, 11.7 mmol) and DMAP (100 mg) in pyridine (10 mL, room temperature, 18 h). Water (1 mL) was added to hydrolyze the excess phthalic anhydride (TLC). Concentration of the mixture followed by normal workup (CH_2Cl_2) and flash chromatography (MeOH/$CHCl_3$, 1 : 9) gave the acid **40** as a colourless oil (1.52 g, 86%), $[\alpha]_D$ +93°. δ_H (300 MHz) 3.40–3.59 (m, H2,3,4,5), 3.56 (s, Me), 4.32 (d, $J_{1,2}$ 7.5, H1), 4.49 (dd, $J_{5,6}$ 4.5, $J_{6,6}$ 12.0, H6), 4.63 (dd, $J_{5,6}$ 2.2, H6), 4.67–4.96 (4 H, m, CH_2Ph), 7.21–7.88 (14 H, m, Ar). δ_C (75.5 MHz) 57.34 (Me), 61.44, 71.94, 81.90, 82.67 (C2, 3, 4, 5), 64.47, 74.81, 75.67 (3 C, C6, *C*H_2Ph), 104.64 (C1), 127.78–138.16 (Ar), 167.56, 170.07 (2 C, C═O). *m*/*z* (FAB) 546.1884 [$(M - H)^{+\bullet}$ requires 546.1876].

*(1*R*,4*S*,5*R*,6*S*)-1-C-(Acetoxymethyl)-4,5,6-tribenzyloxycyclohex-2-en-1-ol **48***

(*a*) Sulfuryl chloride (920 μL, 11.4 mmol) was added dropwise to a solution of 4-methoxybenzyl methylthiomethyl ether (4.15 g, 22.9 mmol) in CH_2Cl_2 (20 mL) at −78°C. After 30 min, TLC analysis showed complete consumption of the 4-methoxybenzyl methylthiomethyl ether. The solution was concentrated to give a colourless oil, presumably chloromethyl 4-methoxybenzyl ether. This oil in THF (20 mL) was treated with Mg (680 mg, 28 mmol) and $HgCl_2$ (50 mg, 0°C, 1 h). The enone **46**[27] (990 mg, 2.4 mmol) was added, and stirring continued (30 min, 0°C). Ac_2O (3.0 mL, 34 mmol) was then added and the mixture stirred (10 min). The mixture was poured into saturated $NaHCO_3$ solution and then stirred and filtered (Celite). Normal workup (CH_2Cl_2) of the filtrate followed by flash chromatography (EtOAc/petrol, 3 : 17) gave an inseparable mixture of, presumably, the acetate **47** and aromatic impurities (^{1}H NMR) as a colourless oil.

(*b*) The above mixture was treated with DDQ (900 mg, 5.6 mmol) in CH_2Cl_2/water (20 mL, 95 : 5; 2 h). Saturated $NaHCO_3$ solution (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with more CH_2Cl_2 (50 mL). The combined organic extracts were dried, filtered, and concentrated to give a dark oil. This oil was purified by flash chromatography (EtOAc/petrol, 1 : 3) to give the acetate **48** as a colourless oil (720 mg, 62%), $[\alpha]_D$ +24° (Found C 74.0, H 6.6. $C_{30}H_{32}O_6$ requires C 73.8, H 6.6%). δ_H (300 MHz) 2.04 (s, Ac), 3.72 (d, $J_{5,6}$ 9.8, H6), 3.92 (dd, $J_{4,5}$ 6.6, H5), 4.11 (d, $J_{7,7}$ 11.4, H7), 4.17 (m, H4), 4.47 (d, H7), 4.62–4.93 (6 H, m, CH_2Ph), 5.61 (dd, $J_{2,3}$ 10.4, $J_{2,4}$ 2.0, H2), 5.78 (dd, $J_{3,4}$ 2.5, H3), 7.21–7.47 (15 H, m, Ar). δ_C (75.5 MHz) 20.94 (Me), 67.65, 72.16, 74.96, 75.49 (4 C, C7, *C*H_2Ph), 74.60 (C1), 79.15, 81.34, 83.65 (C4, 5, 6), 127.74–138.35 (C2, 3, Ar), 171.08 (C═O).

*(1*R*,4*S*,5*R*,6*S*)-4,5,6-Tribenzyloxy-1-C-(hydroxymethyl)cyclohex-2-en-1-ol **49***

A small piece of Na was added to the acetate **48** (540 mg) in MeOH (5 mL, 0°C) and the mixture was stirred (room temperature, 1 h), before being neutralized (Dowex 50W-X8, H^+) and filtered. The filtrate was concentrated to give a yellow oil. This oil was filtered through a plug of silica gel (EtOAc/petrol, 1 : 1) to give the diol **49** as a colourless oil

(450 mg), $[\alpha]_D$ +48°. The ^{1}H NMR (200 MHz) spectrum was consistent with that reported.[30]

*{Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-6-(hydrogen benzene-1,2- dicarboxylate)-β-*D*-glucoside, Ester with* C-*[(1′*R*,4′*S*,5′*R*,6′*S*)-1′-Acetoxy-4′,5′,6′-tribenzyloxycyclohex-2′-enyl]methanol} **38***

The diol **49** (230 mg, 0.48 mmol) and the acid **40** (330 mg, 0.60 mmol) were treated with DCC (125 mg, 0.60 mmol) and DMAP (60 mg, 0.48 mmol) in CH_2Cl_2 (3 mL). After 2 h, TLC analysis indicated the complete consumption of the diol. Acetic acid (140 μL, 2.4 mmol) and more DCC (500 mg, 2.5 mmol) and DMAP (300 mg, 2.5 mmol) were then added and the solution was left for a further 5 h. Pre-adsorbtion onto silica gel, followed by purification on a short column of silica gel (EtOAc/toluene, 1 : 9), gave an oil that was further purified by flash chromatography (EtOAc/petrol, 1 : 4) to give the azide **38** as a colourless oil (370 mg, 74%), $[\alpha]_D$ +77°. δ_H (600 MHz) 1.84 (s, Ac), 3.38–3.42 (m, H5), 3.44 (dd, $J_{1,2}$ 7.9, $J_{2,3}$ 8.6, H2), 3.50–3.57 (m, H3,4), 3.53 (s, OMe), 3.97 (dd, $J_{4',5'}$ 7.7, $J_{5',6'}$ 10.4, H5′), 4.28 (d, H1), 4.33 (ddd, $J_{2',4'} \approx J_{3',4'}$ 2.3, H4′), 4.51 (dd, $J_{5,6}$ 5.0, $J_{6,6}$ 12.0, H6), 4.55, 4.87 (2 H, ABq, J 11.3, H7′), 4.57 (d, H6′), 4.58 (dd, $J_{5,6}$ 2.2, H6), 4.64–4.93 (10 H, m, CH_2Ph), 5.74 (dd, $J_{2',3'}$ 10.5, H2′), 5.89 (dd, H3′), 7.25–7.78 (m, Ar). δ_C (150 MHz) 21.86 (CO*Me*), 57.15 (OMe), 61.69 (C4), 64.48 (C6), 66.60 (C7′), 71.95 (C5), 72.17, 74.76, 75.36, 75.61, 75.62 (5 C, CH_2Ph), 79.79 (C6′), 80.26 (C4′), 81.97 (C2), 82.76 (C3), 82.88 (C5′), 83.66 (C1′), 104.63 (C1), 127.52–138.34 (C2′, 3′, Ar), 166.50, 167.25, 169.77 (3 C, C═O). m/z (FAB) 1018.4028 [(M + H)$^{+\bullet}$ requires 1018.4126].

*{Methyl 4-Amino-2,3-di-*O*-benzyl-4-deoxy-6-(hydrogen benzene-1,2-dicarboxylate)-β-*D*-glucoside, Ester with* C-*[(1′*R*,4′*S*,5′*R*,6′*S*)-1′-Acetoxy-4′5′6′-tribenzyloxycyclohex-2′-enyl]methanol} **50***

The azide **38** (100 mg, 0.10 mmol) was treated with propane-1,3-dithiol (100 μL, 1.0 mmol) and Et_3N (140 μL, 1.0 mmol) in MeOH (5 mL, 8 h). The solution was concentrated to give an orange oil, which was purified by flash chromatography (EtOAc/petrol/Et_3N, 20 : 79 : 1, then EtOAc/petrol/EtOH/Et_3N, 40 : 54 : 5 : 1) to give the amine **50** as a colourless oil (80 mg, 82%), $[\alpha]_D$ +23°. δ_H (300 MHz) 1.84 (s, Ac), 2.85 (dd, $J_{3,4} \approx J_{4,5}$ 9.6, H4), 3.30 (dd, $J_{2,3}$ 9.6, H3), 3.36–3.42 (m, H5), 3.43 (dd, $J_{1,2}$ 7.7, H2), 3.55 (s, OMe), 3.99 (dd, $J_{4',5'}$ 7.7, $J_{5',6'}$ 10.4, H5′), 4.32 (d, H1), 4.27–4.34 (m, H4′), 4.48–4.99 (15 H, m, H6, 6′, 7′, CH_2Ph), 5.73 (dd, $J_{2',3'}$ 10.4, $J_{2',4'}$ 2.2, H2′), 5.89 (dd, $J_{3',4'}$ 2.1 Hz, H3′), 7.25–7.78 (m, Ar). δ_C (75.5 MHz) 21.84 (CO*Me*), 52.74 (C4), 57.05 (OMe), 64.93, 66.57 (C6, 7′), 72.25, 74.55, 75.22, 75.36, 75.57 (5 C, CH_2Ph), 74.77, 79.76, 80.16, 82.43, 82.89, 89.83 (C2, 3, 5, 4′, 5′, 6′), 83.58 (C1′), 105.21 (C1), 127.13–138.23 (C2′, 3′, Ar), 166.55, 167.67, 169.76 (3 C, C═O). m/z (FAB) 992.4227 [(M + H)$^{+\bullet}$ requires 992.4221].

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