An Enantiospecific Synthesis of Allosamizoline

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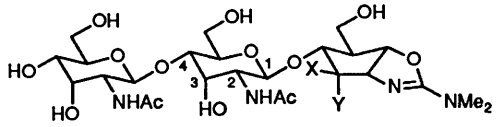
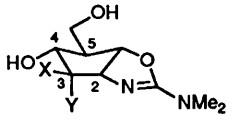
An enantiospecific synthesis of allosamizoline **4**, the aglycone of the chitinase inhibitor allosamidin **3**, has been achieved, starting from readily available glucosamine. The key step in the synthesis involves the cyclisation of a carbon-centred radical onto a suitably positioned oxime ether group, thus effectively converting a carbohydrate derivative into a highly functionalised cyclopentane.

The importance of chitin as a structural component in both fungal cell walls and insect exoskeleton means that chemical agents able to interfere with either its biosynthesis or degradation might be valuable as fungicides or insecticides. In 1986 Sakuda *et al.* reported the isolation of a novel compound from mycelial extracts of *Streptomyces* sp. 1713, named allosamidin, and originally formulated as **1**, which shows potent chitinase inhibitory activity.[1] The paucity of the supply of allosamidin from natural sources, along with the novel structure of the compound, which incorporates a synthetically challenging aminocyclitol **2**, encouraged us to devise a synthesis of this target.

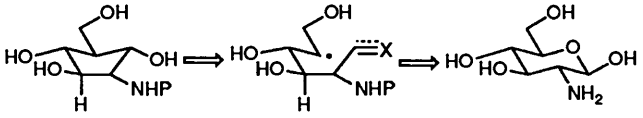
During the course of our studies the structure of allosamidin was revised to **3** (and hence **2** to **4**) but, as will be seen below, our synthetic design is flexible enough to allow the synthesis of either diastereoisomer.[2] Herein, we describe in full our synthetic efforts in this area which have resulted in a concise enantiospecific route to the aminocyclitol **4**, called allosamizoline.[3–7]



1 X = H, Y = OH
3 X = OH, Y = H



2 X = H, Y = OH
4 X = OH, Y = H



P = amine protection ⋯X ≡ C=C, C=O / C≡N, C=NR

Scheme 1

Results and Discussion

The originally proposed structure **1** consists of a disaccharide, made up of two allosamine units, β-linked to the aminocyclitol **2**. Our synthetic analysis began with the observation that the configurations at the four contiguous asymmetric centres, C-2 to C-5, in allosamine bear an obvious relationship to those at the corresponding centres in the aminocyclitol. Thus, a method which allowed the linking of the anomeric carbon of allosamine to C-5, with retention of configuration at the latter centre, would enable the conversion of the sugar into a cyclitol ideal for conversion through into **2**. With the recognition that the configuration at C-3 of the aminocyclitol † is actually β as in **4**, this analysis looks even more appealing since the starting sugar required is simply glucosamine.

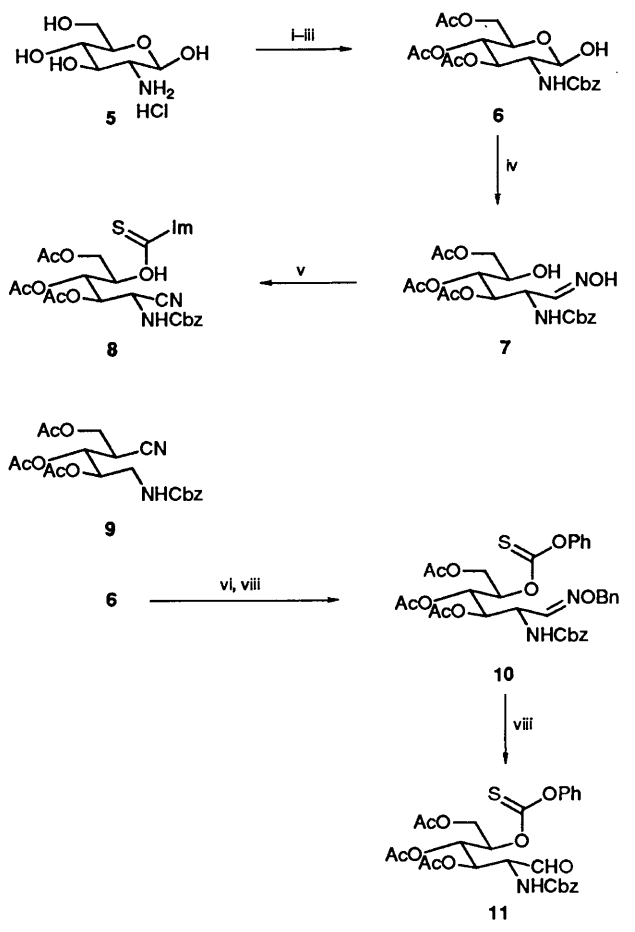
Our choice of a radical cyclisation approach to the problem of the carbohydrate to carbocycle conversion was made bearing in mind the suitability of carbon-centred radicals for the preparation of highly functionalised five-membered rings.[8] Significant contributions have recently been made in this area, for example by Rajanbabu, further convincing us of the viability of this approach.[9] We were also very attracted to the possibility of using an aldehyde as the radical acceptor in the key cyclisation, as described by Fraser-Reid,[10] since this appeared to offer the most attractive way of establishing the desired secondary alcohol at C-1 (Scheme 1).

As shown, a number of alternative groups were also considered as suitable acceptors for a carbon-centred radical, and might give cyclopentane products which could be elaborated to allosamizoline. In the event, we examined the use of aldehyde, nitrile and oxime ether groups in this chemistry; the less accessible alkyne, which could furnish the desired cyclic alcohol following cyclisation, ozonolysis and reduction, was not prepared.[11]

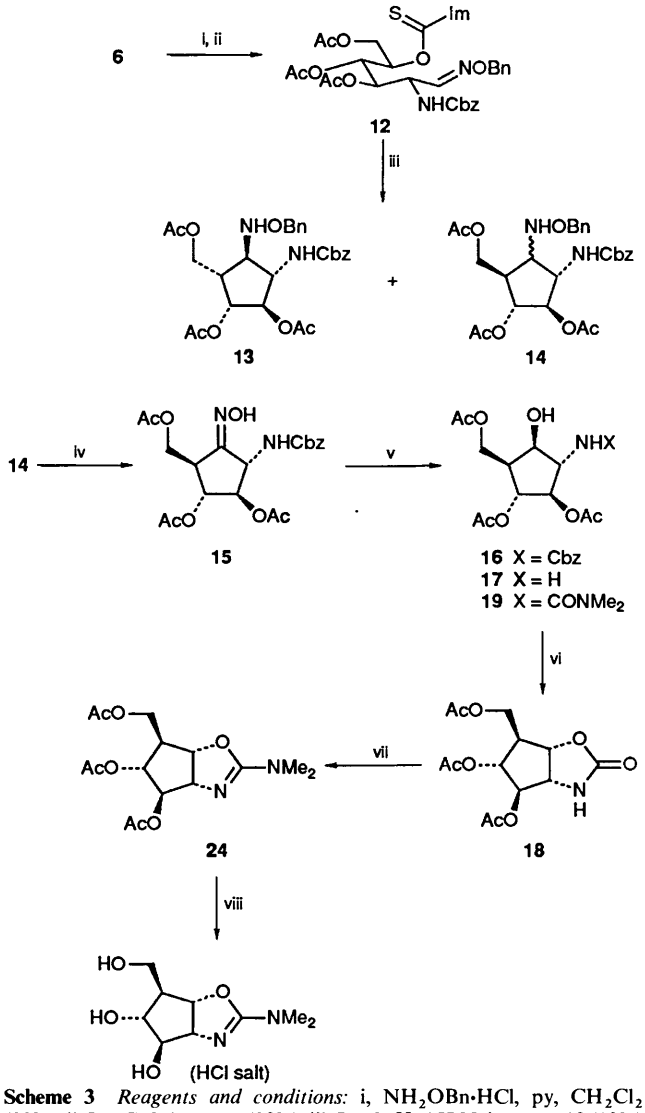
Our synthesis starts with glucosamine hydrochloride **5**, which was converted by standard procedures into the *N*-Cbz tri-*O*-acetyl sugar **6** in 69% overall yield.[12,13] With this material available in quantity the first real problem was to trap the sugar in an open-chain form suitable for the establishment of the radical-generating group at C-5 and some type of acceptor at C-1. Treatment of **6** with NH_2OH·HCl gave an open-chain oxime **7**, which, when treated with 1,1′-thiocarbonyldiimidazole (TCDI), gave the nitrile **8**. Efforts to cyclise this compound under standard radical conditions [syringe-pump addition of Ph_3SnH and azoisobutyronitrile (AIBN) to **8** in refluxing benzene] were unrewarding, spectroscopic evidence pointing to the formation of transposed nitrile **9** in very low yield by a process described previously by Beckwith (Scheme 2).[14]

Alternatively, reaction of **6** with the *O*-benzyl ether of hydroxylamine, followed by derivatisation of the liberated secondary alcohol with *o*-phenyl chlorothioformate gave **10**.[15] Treatment of this compound with camphorsulfonic acid (CSA) in the presence of aqueous formaldehyde then gave the aldehyde **11**. In this acidic hydrolysis step it proved crucial to use the phenoxy(thiocarbonyl)oxy group instead of the more acid-labile imidazolylthiocarbonyloxy group. It was hoped that compound **11** could be cyclised to give the desired cyclo-

† The numbering system shown is used for ease of comparison between the sugar and the cyclitol.



Scheme 2 *Reagents:* i, CbzCl, $NaHCO_3$, H_2O (96%); ii, Ac_2O, Et_3N, DMAP, THF (82%); iii, $(NH_4)_2CO_3$, MeOH, THF (88%); iv, NH_2OH·HCl, py, MeOH (78%); v, TCDI, CH_2Cl_2 (58%); vi, NH_2OBn·HCl, py, CH_2Cl_2 (88%); vii, PhO(Cl)C=S, py, CH_2Cl_2 (78%); viii, HCHO, H_2O, THF, CSA (74%)



Scheme 3 *Reagents and conditions:* i, NH_2OBn·HCl, py, CH_2Cl_2 (88%); ii, Im_2C=S, benzene (82%); iii, Bu_3SnH, AIBN, benzene **13** (12%) and **14** (54%); iv, MCPBA, Na_2CO_3, EtOAc (79%); v, O_3, CH_2Cl_2, −40 °C; MeOH, $NaBH_4$, −40 °C to RT; vi, $SOCl_2$ (82%); vii, Et_3OBF_4, CH_2Cl_2; Me_2NH, CH_2Cl_2 (80%); viii, NaOMe, MeOH; HCl (98%)

pentanol as described by Fraser-Reid. However, again we found we were unable to effect the desired conversion, mixtures of aldehydic products being produced, presumably by cleavage of an intermediate cyclic alkoxyl radical.

The failure of the two attempted cyclisations described above presumably reflects the ability of the intermediate cyclised oxygen- or nitrogen-centred radicals to undergo cleavage to give a radical α to the stabilising *N*-Cbz group. In reactions involving the aldehyde **11** we attempted to increase the likelihood of hydrogen atom donation to the cyclic alkoxyl radical by increasing the concentration of Bu_3SnH, or by using THF as the solvent, but with little effect.

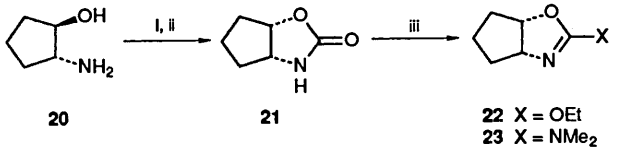
We next focused our attention on a report by Bartlett *et al.* describing successful cyclisations of radicals onto oxime ethers.[16] We were pleased to find that treatment of the thiocarbonylimidazolide **12**, easily available from **6**, with Bu_3SnH and AIBN under reflux in benzene, resulted in clean conversion into a mixture of diastereoisomeric products **13** and **14** (Scheme 3).

The configuration shown for the minor isomer **13**, obtained in 12% yield, is based on the previous results of Bartlett *et al.* The configuration of the major product **14**, obtained as a mixture of epimers at C-1 in 54% yield, was expected to be as shown, and was proven by subsequent conversion of this mixture to allosamizoline.

The conversion of the benzyloxyamino group in **14** into the desired secondary alcohol proved to be a major stumbling block, and we were surprised to find so few methods available for this type of transformation in the literature.[17] The best method tried involves initial oxidation of the mixture of benzyloxyamines with MCPBA to give oxime **15** in 79% yield,[18] followed by reaction with ozone and direct reductive work-up.[19] The latter step proved problematic, and, despite experimentation with the solvent and temperature used for the ozonolysis, the overall yield for the conversion of **15** into the alcohol **16** is only in the range 20–40% (taking into account recovered oxime). However, the shortness of the synthetic sequence, combined with the good to excellent yields obtained in all the other steps allowed us to continue the synthesis on a reasonable scale. The configuration at C-1 in **16** could not be determined with certainty at this stage but was later assigned on the basis of subsequent conversions, *vide infra*.

We felt that it should be possible to carry out the remaining conversion of the vicinal hydroxy and protected amine groups in **16** into the desired oxazoline system whatever the configuration at C-1. Removal of the carbamate protecting group from **16** gave a rather sensitive amine **17**, which was not purified. Attempts to convert this material into oxazolidinone **18** by treatment with triphosgene were unsuccessful, and gave the first indication of the *trans* relationship of the amine and alcohol functions. Efforts to prepare the urea **19** by treatment of the crude amine **17** with dimethylcarbamoyl chloride were also unsuccessful.

At this stage we decided to examine a number of protocols for the preparation of the required dimethylaminooxazoline using the simple *trans*-amino alcohol **20**. The route which proved most satisfactory involves treatment of the benzyl carbamate derived from **20** with thionyl chloride to give oxazolidinone **21** (Scheme 4).



20 **21** **22** X = OEt, **23** X = NMe_2

Scheme 4 *Reagents:* i, $PhCH_2OCOCl$, NaOH (60%); ii, $SOCl_2$ (92%); iii, $Et_3O{\cdot}BF_4$; Me_2NH (63%)

Treatment of this compund with $Et_3O{\cdot}BF_4$ gave an intermediate ethoxyoxazoline **22**, which was treated *in situ* with a solution of Me_2NH in order to effect conversion into **23**. A similar conversion of an oxazolidinone into a dimethylaminooxazoline was used by Trost and Van Dranken in their synthesis of racemic allosamizoline.[4]

We were delighted to find that this sequence could be readily applied to our synthetic intermediate **16**, which, on reaction with thionyl chloride, gave the oxazolidinone **18** in 82% yield. This approach is especially attractive since it obviates the need for amine deprotection and incorporates part of the original carbamate protecting group into the final target. We assume that this conversion follows the same stereochemical course as in the model reaction, involving inversion at C-1, which establishes the *trans* stereochemistry shown for **16**. Subsequent treatment of **18** with $Et_3O{\cdot}BF_4$ in CH_2Cl_2 followed by Me_2NH gave the desired allosamizoline triacetate **24** in 80% overall. Subsequent saponification of this compound with NaOMe then gave allosamizoline hydrochloride, $[\alpha]_D^{23}$ −21.7 (*c* 0.9 in H_2O) {lit.,[1] $[\alpha]_D$ −22.2 (*c* 0.5 in H_2O)} in 98% yield.

Some comment on the ^1H NMR spectra of intermediates **18** and **24**, and the final product, allosamizoline **4** hydrochloride salt, is warranted. Firstly, we were initially somewhat dismayed to find that the ^1H NMR spectrum of our sample of allosamizoline triacetate **24**, recorded in $CHCl_3$, did not match precisely that reported by Sakuda *et al.*[2] Most noticeable was the chemical shift of the two NMe groups which are coincident at δ 2.94 in our sample, compared to δ 3.03 in the reported spectrum. Although the overall appearance of our spectrum, including coupling constants, was very close to that expected, small discrepancies in chemical shift (all less than 0.1 ppm) were a cause for concern. We were, therefore, pleased to find that the ^1H NMR spectrum of our allosamizoline hydrochloride, *measured at* 298 K in D_2O, was totally in accord with that reported previously. It should be noted, however, that the chemical shifts measured in D_2O at lower temperature, *e.g.* 287 K, are all shifted upfield by *ca.* 0.1 ppm relative to DOH. Soon after this work was completed, Nakata *et al.*[6] described a synthesis of allosamizoline, and included ^1H NMR data for oxazolidinone **18** which are completely in accord with our findings.

The synthesis described in this paper further underlines the usefulness of radical cyclisations in natural product synthesis. The route described here should be useful for accessing allosamizoline as well as a range of related compounds simply by choice of the appropriate starting sugar.

Experimental

Melting points for solid products were determined using a Reichert Microscope apparatus, and are uncorrected. Products without melting points are colourless oils. IR spectra were recorded on a Perkin-Elmer 298, Philips PU96706 or Pye Unicam SP3-100 grating spectrophotometer. NMR spectra were recorded on a Bruker WP80, Bruker AM250 or Bruker AM400 machine, with Me_4Si as internal standard unless otherwise stated; *J*-values are given in Hz. Mass spectra were recorded on AEI 902 or VG micromass 70E spectrometers. Microanalyses were performed at the microanalytical laboratory at Nottingham University. Optical rotations were measured on Optical Activity, model A1000, and JASCO, model DIP-370 instruments and $[\alpha]_D$ values are expressed in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Keiselgel 60 (230–400 mesh). Solvents were purified by standard techniques before use.

2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranose **6**.—(*a*) 2-Benzyloxycarbonylamino-2-deoxy-D-glycopyranose was prepared from glucosamine hydrochloride, using the method of Chargaff and Bovarnick,[12] in 96% yield, m.p. 215 °C (lit.,[12] 214 °C).

(*b*) *1,3,4,6-Tetra-O-acetyl-2-benzyloxycarbonylamino-2-deoxy-D-glucopyranoside.* To a suspension of the *N*-protected sugar obtained in (*a*) (70 g, 224 mmol) in THF (140 cm^3) was added triethylamine (140 cm^3, 1.0 mol), acetic anhydride (140 cm^3, 1.5 mol) and DMAP (200 mg, 1.6 mmol) at 0 °C. The resultant solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (200 cm^3) and extracted with ethyl acetate (3 × 200 cm^3). The combined organics were washed with dilute HCl (3 × 200 cm^3), saturated aqueous sodium hydrogen carbonate (3 × 200 cm^3) and brine (200 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the *title compound* as a 1:1 mixture of anomers, which crystallised from ether at 0 °C (93.34 g, 87%). An analytical sample was recrystallised from aqueous methanol, m.p. 143–147 °C (from MeOH–H_2O), $[\alpha]_D^{26}$ +15.8 (*c* 0.7 in $CHCl_3$) (Found: C, 54.9; H, 5.7; N, 3.05. $C_{22}H_{27}NO_{11}$ requires C, 54.9; H, 5.65; N, 2.9%); ν_{max}($CHCl_3$ solution)/cm^{-1} 1755 and 1376; δ_H(250 MHz; $CDCl_3$) (α anomer) 1.94 (3 H, s, OAc), 2.03 (6 H, s, 2 × OAc), 2.08 (3 H, s, OAc), 3.82 (1 H, m), 3.93–4.12 (2 H, m), 4.27 (1 H, m), 5.06–5.31 (5 H, m), 5.69 (1 H, d, *J* 8.8, 1-H) and 7.32 (5 H, s, aryl CH), (β anomer) 1.93 (3 H, s, OAc), 2.03 (3 H, s, OAc), 2.08 (3 H, s, OAc), 2.16 (3 H, s, OAc), 3.98–4.08 (2 H, m), 4.18–4.30 (2 H, m), 5.00–5.31 (5 H, m), 6.20 (1 H, d, *J* 3.6) and 7.34 (5 H, s, aryl CH); δ_C(22.5 MHz; $CDCl_3$) (α anomer) 20.5 (q, CH_3C=O), 20.6 (q, CH_3C=O), 54.9 (d, 2-C), 61.8 (t), 66.9 (t), 68.3 (d), 72.5 (d), 72.8 (d), 92.6 (d, 1-C), 128.0 (d, aryl CH), 128.1 (aryl CH), 128.5 (aryl CH), 136.4 (aryl C), 155.9 (s, NHC=O), 169.4 (s, CH_3C=O), 170.6 (s, CH_3C=O) and 170.8 (s, CH_3C=O), (β anomer) 20.4 (q, CH_3C=O), 20.5 (q, CH_3C=O), 20.7 (q, CH_3C=O), 52.7 (d, 2-C), 61.4 (t), 67.1 (t), 67.5 (d), 69.5 (d), 70.5 (d), 90.7 (d, 1-C), 128.1 (d, aryl CH), 128.2 (d, aryl CH), 128.4 (d, aryl CH), 135.8 (d, aryl C), 155.5 (s, NHC=O), 168.5 (s, CH_3C=O), 169.1 (s, CH_3C=O), 170.5 (s, CH_3C=O) and 171.1 (s, CH_3C=O) (Found: $M^+ - COCH_3$, 438.1397. $C_{20}H_{24}NO_{10}$ requires *M*, 438.1397).

(*c*) *2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranose* **6** *using the method of Mikamo.*[13] Powdered ammonium carbonate (46 g, 293 mmol) was added to solution of the tetraacetate obtained in (*b*) (31.06 g, 75 mmol) in THF (75 cm^3) and methanol (150 cm^3). The suspension was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue dissolved in chloroform (300 cm^3). The solution was washed with water (300 cm^3) and brine (150 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give an orange syrup. Recrystallisation from ether–hexanes gave the *title compound* **6** as a white crystalline solid (27.5 g, 84%), m.p. 145–147 °C (from ether), $[\alpha]_D^{26}$ +44.5 (*c* 0.58 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 3400, 2960, 1740, 1705, 1540, 750 and 710; δ_H(250 MHz; $CDCl_3$)

1.90 (3 H, s, OAc), 2.02 (3 H, s, OAc), 2.09 (3 H, s, OAc), 4.16–4.32 (2 H, m), 4.38–4.48 (2 H, m), 5.17–5.68 (7 H, m) and 7.33 (5 H, s, aryl CH); δ_C(100 MHz; $CDCl_3$) 20.68 (q, CH_3C=O), 20.72 (q, CH_3C=O), 20.9 (q, CH_3C=O), 54.1 (d, 2-C), 62.2 (t), 67.1 (t), 67.8 (d), 68.5 (d), 71.0 (d), 92.0 (d, 1-C), 128.2 (d, aryl CH), 128.3 (d, aryl CH) 128.6 (d, aryl CH), 136.3 (s, aryl C), 156.0 (s, NHC=O), 169.6 (s, CH_3C=O), 171.2 (s, CH_3C=O) and 171.3 (s, CH_3C=O); (Found: $M^+ - H_2O$, 421.1366. $C_{20}H_{23}NO_9$ requires *M*, 421.1370).

2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-D-*glucose Oxime* **7**.—To a solution of **6** (1.53 g, 3.5 mmol) in methanol (20 cm^3) was added pyridine (0.7 cm^3, 9 mmol) and hydroxylamine hydrochloride (370 mg, 5.3 mmol) and the solution heated to reflux for 2 h. The reaction mixture was allowed to cool and then poured into dilute HCl (50 cm^3). The solution was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic extracts were washed with aqueous sodium hydrogen carbonate (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue gave the *title oxime* **7**, which was an 85:15 mixture of isomers, as a white foam (1.24 g, 78%), $[\alpha]_D^{31}$ +18.7 (*c* 0.66 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3370, 2962, 1741, 1230, 1045, 742 and 700; δ_H(major isomer) (250 MHz; $CDCl_3$) 2.05 (6 H, s, 2 × OAc), 2.10 (3 H, s, OAc), 3.70 (1 H, br s), 4.10–4.12 (2 H, m), 4.68 (1 H, m), 5.10–5.20 (4 H, m), 5.50–5.60 (1 H, m), 5.76 (1 H, d, *J* 8.6), 7.36 (5 H, s, Ph), 7.46 (1 H, d, *J* 3.8, *CH*=NOH) and 8.20 (1 H, br s, CH=NO*H*); δ_C(major isomer) (22.5 MHz; $CDCl_3$) 20.7 (q, 3 × CH_3C=O), 51.5 (d, 2-C), 63.1, 64.9, 67.3, 68.4, 70.3, 71.2, 128.2 (d, aryl CH), 128.6 (d, aryl CH), 136.2 (s, aryl C), 147.5 (d, 1-C), 156.1 (s, NHC=O), 170.4 (s, CH_3C=O), 171.0 (s, CH_3C=O) and 171.3 (s, CH_3C=O); *m*/*z* (FAB) 455 (M^+ + H, 4%) and 91 (100%).

2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-5-*imidazol*-1-*ylthiocarbonyloxy*-D-*glucononitrile* **8**.—To a solution of the oxime **7** (1.25 g, 2.8 mmol) in dichloromethane (40 cm^3) was added 1,1′-thiocarbonyldiimidazole (560 mg, 3.1 mmol). The reaction mixture was stirred at room temperature, under an atmosphere of nitrogen, for 1 h before further addition of 1,1′-thiocarbonyldiimidazole (540 mg, 3.0 mmol). Stirring was continued for 6 h. The reaction mixture was washed with dilute HCl (50 cm^3) and saturated aqueous sodium hydrogen carbonate (40 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow syrup. Flash chromatography of the latter gave the *title compound* **8** as an off-white foam (865 mg, 58%), ν_{max}(KBr disc)/cm^{-1} 3330, 2962, 2253, 1733, 740 and 695; δ_H(250 MHz; $CDCl_3$) 2.08 (3 H, s, OAc), 2.15 (3 H, s, OAc), 2.25 (3 H, s, OAc), 4.39–4.53 (2 H, m), 5.11–5.23 (4 H, m), 5.67 (1 H, d, *J* 8.0), 5.94–6.00 (2 H, m), 7.07 (1 H, m), 7.38 (5 H, s, Ph), 7.55 (1 H, m) and 8.28 (1 H, m, N=CH–N); δ_C(22.5 MHz; $CDCl_3$) 20.4 (q, CH_3C=O), 20.7 (q, CH_3C=O), 42.7 (d, 2-C), 60.6 (t), 67.3 (t), 67.6 (d), 68.0 (d), 68.2 (d), 77.3 (d), 115.5 (s, CN), 118.2 (d, imidaz. CH), 128.3 (d, aryl CH), 128.5 (d, aryl CH), 128.6 (d, aryl CH), 131.2 (d, imidaz. CH), 135.4 (s, aryl C), 137.0 (d, imidaz. CH), 155.0 (s, NHC=O), 169.2 (s, CH_3C=O), 170.2 (s, CH_3C=O), 170.9 (s, CH_3C=O) and 182.7 (s, C=S); *m*/*z* 418 [M^+ − HOC(S)Im, 2%] and 91 (100%).

2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-5-*phenoxy*(*thiocarbonyl*)*oxy*-D-*glucose* O-*Benzyl Oxime* **10**.—(*a*) 2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-D-*glucopyranose* O-*benzyl oxime ether*. To a solution of the glucosamine derivative **6** (19.8 g, 45 mmol) in dichloromethane (230 cm^3) was added dry pyridine (11.5 cm^3, 143 mmol) and *O*-benzylhydroxylamine hydrochloride (11.0 g, 68 mmol). The suspension was stirred at room temperature under an atmosphere of dry nitrogen for 7 days. The reaction mixture was poured into dilute hydrochloric acid (400 cm^3) and extracted with ethyl acetate (300 cm^3). The organic phase was washed with brine (300 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Crystallisation of the residue from ether at 0 °C gave the *title oxime ether* as a white crystalline solid (21.5 g, 88%), m.p. 98–100 °C (from ether); $[\alpha]_D^{26}$ +15.4 (*c* 0.21 in $CHCl_3$); (Found: C, 59.2; H, 6.0; N, 5.05. $C_{27}H_{32}N_2O_{10}$ requires C, 59.55; H, 5.9; N, 5.1%); ν_{max}(KBr disc)/cm^{-1} 3414, 3348, 3033, 2921, 1757, 1537, 1050, 739 and 696; δ_H(250 MHz; $CDCl_3$) 2.00 (3 H, s, OAc), 2.01 (3 H, s, OAc), 2.07 (3 H, s, OAc), 3.38 (1 H, d, *J* 6.4, OH), 3.77 (1 H, m, 5-H), 4.09 (2 H, d, *J* 4.0, 6-H), 4.76 (1 H, m, 2-H), 5.03 (2 H, s, CH_2Ph), 5.14 (2 H, s, CH_2Ph), 5.17 (1 H, dd, *J* 8.8 and 3.0, 4-H), 5.50–5.54 (2 H, m, 3-H and NH), 7.30–7.37 (10 H, m, Ph) and 7.48 (1 H, d, *J* 3.5, 1-H); δ_C(22.5 MHz; $CDCl_3$) 20.3 (q, CH_3C=O), 20.5 (q, CH_3C=O), 51.5 (d, 2-C), 65.0 (t), 67.1 (t), 68.2 (d), 70.2 (d), 70.8 (d), 76.3 (t), 128.0 (d, aryl CH), 128.3 (d, aryl CH), 136.2 (s, aryl C), 137.0 (s, aryl C), 145.9 (d, 1-C), 155.8 (s, NHC=O), 169.8 (s, CH_3C=O), 170.4 (s, CH_3C=O) and 170.9 (s, CH_3C=O); *m*/*z* (FAB) 545 (M^+ + H, 6%).

(*b*) 2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-5-*phenoxy*(*thiocarbonyl*)*oxy*-D-*glucose* O-*Benzyl Oxime* **10**.—To a solution of the oxime ether obtained in (*a*) (716 mg, 1.32 mmol) in dichloromethane (25 cm^3) at 0 °C was added *O*-phenyl chlorothioformate (2.0 g, 11.8 mmol) and pyridine (4 cm^3, 50 mmol). The stirred solution was allowed to warm to room temperature overnight under an atmosphere of nitrogen after which it was poured into dilute HCl (50 cm^3) and extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (20 to 50% ethyl acetate in light petroleum) gave the title compound **10** as a foam (696 mg, 78%), $[\alpha]_D^{31}$ +32.4 (*c* 0.29 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3350, 2970, 1760, 1200, 740 and 700; δ_H(250 MHz; $CDCl_3$) 1.98 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.07 (3 H, s, OAc), 4.26 (1 H, d, *J* 12.7, 6-H), 4.60 (1 H, d, *J* 12.7, 6′-H), 4.70 (1 H, br s), 5.04 (2 H, s, OCH_2Ph), 5.12 (2 H, s, OCH_2Ph), 5.38 (1 H, d, *J* 8.6), 5.54 (1 H, d, *J* 6.6), 5.65 (2 H, s) and 7.12–7.48 (16 H, m, aryl CH and 1-H); δ_C(22.5 MHz; $CDCl_3$), 20.4 (q, CH_3C=O), 20.5 (q, CH_3C=O), 20.6 (q, CH_3C=O), 51.0 (d, 2-C), 60.6 (t), 67.0 (t), 67.6 (d), 69.4 (d), 76.4 (t), 78.0 (d), 121.7 (d, aryl CH), 126.6 (d, aryl CH), 128.4 (d, aryl CH), 129.4 (d, aryl CH), 136.2 (s, aryl C), 136.9 (s, aryl C), 145.6 (d, CH=N), 153.5 (s, aryl C), 155.5 (s, NHC=O), 169.5 (s, CH_3C=O), 169.6 (s, CH_3C=O), 170.2 (s, CH_3C=O) and 194.2 (s, C=S); *m*/*z* (FAB) 681 (M^+ + H, 6%), 527 (32%) and 91 (100%).

2-*Benzyloxycarbonylamino*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-5-*phenoxy*(*thiocarbonyl*)*oxy*-D-*glucose* **11**.—To a solution of compound **10** (200 mg, 0.29 mmol) in THF (3 cm^3) was added 37% aqueous formaldehyde (2 cm^3) and camphorsulfonic acid (270 mg, 1.16 mmol). The solution was stirred at room temperature until TLC indicated absence of starting material. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with ether (20 cm^3). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude aldehyde **11** as a syrup (125 mg, 74%), ν_{max}(film)/cm^{-1} 3376, 3034, 2957, 1732, 1591, 1064 and 695; δ_H(80 MHz; $CDCl_3$) 2.00 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.11 (3 H, s, OAc), 4.32–5.75 (9 H, m), 7.06–7.43 (10 H, m, Ph) and 9.70 (1 H, d, *J* 3.3, 1-H); δ_C(22.5 MHz; $CDCl_3$), 20.5 (q, CH_3C=O), 20.6 (q, CH_3C=O), 20.8 (q, CH_3C=O), 60.3, 60.9, 67.8, 68.1, 69.0, 78.2, 83.0, 122.0 (d, aryl CH), 127.0 (d, aryl CH), 128.4 (d, aryl CH), 128.8 (d, aryl CH), 129.7 (d, aryl CH), 136.1 (s, aryl C), 137.8 (s, aryl C), 153.7 (s, aryl C), 156.1 (s, NHC=O), 169.5 (s, CH_3C=O), 169.8 (s, CH_3C=O), 170.6 (s, CH_3C=O), 194.5 (s) and 196.0 (s); *m*/*z* (FAB) 576 (M^+ + H, 5%), 422 (55) and 65 (100%).

2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-5-imidazol-1-ylthiocarbonyloxy-D-glucose O-Benzyl Oxime **12**.—(*a*) *2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranose O-Benzyl Oxime ether*. This compound was prepared as described above in the preparation of compound **10**.

(*b*) *2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-5-imidazol-1-ylthiocarbonyloxy-D-glucose O-Benzyl Oxime* **12**. To a solution of the oxime ether obtained in (*a*) (6.34 g, 11.65 mmol) in benzene (100 cm^3) was added 1,1′-thiocarbonyldiimidazole (3.03 g, 17.02 mmol). The solution was heated to reflux under an atmosphere of nitrogen for 3.5 h. The reaction mixture was allowed to cool and then evaporated under reduced pressure. Flash chromatography (20 to 50% ether in dichloromethane) gave the *title imidazolide* **12** as a foam (6.28 g, 82%), $[\alpha]_D^{22}$ +38.3 (*c* 0.23 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1751, 1290 and 970; δ_H(250 MHz; $CDCl_3$), 1.95 (3 H, s, OAc), 2.03 (3 H, s, OAc), 2.07 (3 H, s, OAc), 4.29 (1 H, dd, *J* 12.9 and 5.3, 6-H), 4.46 (1 H, dd, *J* 12.9 and 2.9, 6′-H), 4.67 (1 H, m, 2-H), 5.05 (2 H, s, CH_2Ph), 5.09 (1 H, d, *J* 12.9, C*H*H′Ph), 5.14 (1 H, d, *J* 12.9, CH*H*′Ph), 5.38 (1 H, br d, *J* 8.8, NH), 5.51 (1 H, dd, *J* 6.5 and 3.0, 3-H), 5.84 (1 H, dd, *J* 6.4 and 3.0, 4-H), 5.85 (1 H, m, 5-H), 7.04 (1 H, m), 7.29–7.37 (10 H, m, Ph), 7.45 (1 H, d, *J* 3.8, 1-H), 7.51 (1 H, m) and 8.25 (1 H, m); δ_C(22.5 MHz; $CDCl_3$), 20.9 (q, *C*H_3C=O), 50.9 (d, 2-C), 60.9 (t), 67.0 (t), 68.2 (d), 69.6 (d), 76.2 (t), 78.1 (d), 117.8 (d, imidaz. CH), 127.9 (d, aryl CH), 128.0 (d, aryl CH), 128.2 (d, aryl CH), 130.9 (d, imidaz. CH), 136.0 (s, aryl C), 136.9 (d, imidaz. CH), 145.4 (d, 1-C), 155.5 (s, NHC=O), 169.3 (s, CH_3C=O), 169.4 (s, CH_3C=O), 170.0 (s, CH_3C=O) and 182.8 (s, C=S); *m*/*z* (FAB) 655 (M^+ + H, 5%).

Cyclisation of 2-Benzyloxycarbonylamino-2-deoxy-3,4,6-tri-O-acetyl-5-imidazol-1-ylthiocarbonyloxy-D-glucose O-Benzyl Oxime **12** *with Tributyltin Hydride*.—To a refluxing solution of the imidazolide **12** (6.28 g, 9.60 mmol) in dry benzene (470 cm^3) under an atmosphere of nitrogen was added a solution of tributyltin hydride (6.07 g, 20.8 mmol) and AIBN (672 mg, 2.5 mmol) in benzene (20 cm^3) dropwise over 10 min. The solution was heated under reflux for 3.5 h after which it was allowed to cool and then evaporated under reduced pressure. Flash chromatography (5–15% ether in dichloromethane) of the residue afforded **14** as a 1:1 mixture of epimers at C-1 (2.74 g, 54%), ν_{max}(film)/cm^{-1} 3351, 2954, 1740 and 1233; δ_H(less polar isomer, 250 MHz; $CDCl_3$) 1.98 (3 H, s, OAc), 2.00 (3 H, s, OAc), 2.02 (3 H, s, OAc), 2.36 (1 H, m, 5-H), 3.28 (1 H, m, 1-H), 4.07–4.18 (3 H, m, 6-H, 6-H′ and 2-H) 4.64 (1 H, d, *J* 11.8, NHOC*H*H′Ph), 4.74 (1 H, d, *J* 11.8, NHOCH*H*′Ph), 5.09 [2 H, s, C(O)OCH_2Ph], 5.27–5.51 (2 H, m, 3-H and 4-H), 5.82 (1 H, br s, NH) and 7.35 (10 H, s, aryl CH), (more polar isomer, 270 MHz; $CDCl_3$) 2.02 (3 H, s, OAc), 2.04 (6 H, s, OAc), 2.55 (1 H, m, 5-H), 3.54 (1 H, m, 1-H), 3.99 (1 H, dd, *J* 7.3 and 6.7, 2-H), 4.23 (1 H, dd, *J* 11.2 and 6.1, 6-H), 4.40 (1 H, dd, *J* 11.2 and 6.3, 6′-H), 4.71 (2 H, s, NHOCH_2Ph), 5.07 [1 H, d, *J* 12.4, C(O)OC*H*H′Ph], 5.08 [1 H, d, *J* 12.4, C(O)OCH*H*′Ph], 5.16 (1 H, m, 3-H), 5.27 (1 H, m, 4-H) and 7.34 (10 H, s, aryl CH); δ_C(mixture of isomers, 22.5 MHz; $CDCl_3$) 20.8 (q, 6 × *C*H_3C=O), 42.9 (d, 5-C), 43.5 (d, 5-C), 55.5 (d), 57.2 (d), 59.7 (d), 61.7 (t), 62.1 (t), 63.2 (d) 63.7 (d), 67.0 (t), 74.2 (d), 76.2 (t), 76.9 (t), 79.1 (d), 79.3 (d), 128.0 (d, aryl CH), 128.2 (d, aryl CH), 128.5 (d, aryl CH), 136.2 (s, aryl C), 136.9 (s, aryl C), 137.1 (s, aryl C), 156.1 (s, NHC=O), 170.1 (s, CH_3C=O), 170.3 (s, CH_3C=O), 170.6 (s, CH_3C=O), 170.7 (s, CH_3C=O) and 170.9 (s, CH_3C=O); *m*/*z* 529 (M^+ + H, 11%), 361 (19%), 301 (14%) and 91 (100%), and **13** (608 mg, 12%), $[\alpha]_D^{25}$ −2.1 (*c* 0.7 in $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 1732, 1361 and 976; δ_H(250 MHz; $CDCl_3$) 1.99 (3 H, s, OAc), 2.03 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.71 (1 H, m, 5-H), 3.24 (1 H, m, 1-H), 3.95–4.27 (3 H, m, 6-H, 6′-H and 2-H), 4.72 (2 H, s, NHOCH_2Ph), 5.08 [2 H, s, C(O)OCH_2Ph], 5.11–5.44 (3 H, m, 3-H, 4-H and NH), 6.20 (1 H, vbr s, NH) and 7.35 (10 H, s, aryl CH); δ_C(22.5 MHz; $CDCl_3$) 20.5 (q, 3 × *C*H_3C=O), 40.2 (d, 5-C), 56.1 (d, 2-C), 61.6 (t), 66.0 (d), 66.7 (t), 73.7 (d), 76.7 (t), 78.5 (d), 127.6 (d, aryl CH), 127.9 (d, aryl CH), 128.1 (d, aryl CH), 128.3 (d, aryl CH), 136.1 (s, aryl C), 137.3 (s, aryl C), 156.2 (s, NHC=O), 169.3 (s, CH_3C=O) and 170.3 (s, 2 × CH_3C=O); *m*/*z* (FAB) 529 (M^+ + H, 10%).

2S,3R,4R,5R-2,3,4-Diacetoxy-5-acetoxymethylbenzyloxycarbonylaminocyclopentanone Oxime **15**.—To a solution of the hydroxylamines **14** (2.33 g, 4.4 mmol) in ethyl acetate (40 cm^3) was added sodium carbonate (1.10 g, 10.4 mmol) and 50% MCPBA (1.81 g, 5.2 mmol). The suspension was stirred at room temperature for 1 h. The resultant white paste was diluted with ethyl acetate (100 cm^3) and washed with water (100 cm^3) and brine (100 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (20 to 60% ethyl acetate in light petroleum) of the residue gave the *title oxime* **15** as a white foam (1.51 g, 79%), m.p. 137 °C (from ether), $[\alpha]_D^{30}$ −3.5 (*c* 0.2 in EtOH) (Found: C, 55.2; H, 5.5; N, 6.2. $C_{20}H_{24}N_2O_9$ requires C, 55.0; H, 5.5; N, 6.4%); ν_{max}(KBr disc)/cm^{-1} 3371, 1748, 1529, 1044 and 700; δ_H(250 MHz; $CDCl_3$) 2.06 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.09 (3 H, s, OAc), 3.26 (1 H, m, 5-H), 4.31–4.36 (2 H, m), 4.60–4.80 (2 H, m), 5.11 (2 H, s, CH_2Ph), 5.16–5.35 (2 H, m), 7.33 (5 H, s, aryl CH) and 8.30 (1 H, vbr s, C=NOH); δ_C(67.8 MHz; $CDCl_3$) 20.8 (q, 3 × *C*H_3C=O), 42.8 (d, 5-C), 56.5 (d, 2-C), 61.4 (t), 67.2 (t), 73.5 (d), 77.2 (d), 128.0 (d, aryl CH), 128.2 (d, aryl CH), 128.5 (aryl CH), 136.2 (aryl C), 154.1 (s), 156.0 (s), 170.3 (s, CH_3C=O), 170.8 (s, CH_3C=O) and 170.9 (s, CH_3C=O); *m*/*z* 437 (M^+ + H, 10%) and 91 (100%).

1R,2S,3R,4R,5R,3,4-Diacetoxy-5-acetoxymethyl-2-benzyloxycarbonylaminocyclopentanol **16**.—Ozone was bubbled through a solution of the oxime **15** (700 mg, 1.61 mmol) in dichloromethane (40 cm^3) at −40 °C for 8 h. The reaction mixture was purged with oxygen for 10 min before addition of methanol (40 cm^3) and sodium borohydride (100 mg, 2.6 mmol). The solution was allowed to warm to room temperature and was then evaporated under reduced pressure. The residue was partitioned between water (20 cm^3) and dichloromethane (50 cm^3). The aqueous phase was extracted with dichloromethane (3 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (10–25% ether in dichloromethane) gave recovered oxime **15** (100 mg), and the *title cyclopentanol* **16** as a syrup which crystallised from ether (130 mg, 19%), m.p. 119–121 °C (from ether), $[\alpha]_D^{22}$ +31 (*c* 0.1 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 3429, 3340, 1728, 1694, 1252 and 1038; δ_H(250 MHz; $CDCl_3$) 2.06 (3 H, s, OAc), 2.07 (3 H, s, OAc), 2.09 (3 H, s, OAc), 2.50 (1 H, m, 5-H), 3.80 (1 H, m, 2-H), 4.00–4.26 (3 H, m), 4.44 (1 H, dd, *J* 11.4 and 6.5, 6-H), 5.04 (1 H, dd, *J* 8.0 and 6.7, 3-H), 5.10 (1 H, d, *J* 12.2, C*H*H′Ph), 5.11 (1 H, d, *J* 12.2, CH*H*′Ph), 5.31 (1 H, m, 4-H), 5.77 (1 H, br s) and 7.35 (5 H, s, Ph); δ_C(22.5 MHz; $CDCl_3$) 20.8 (q, CH_3C=O), 44.6 (d, 5-C), 61.2 (t), 63.4 (d, 2-C), 67.4 (t), 74.0 (d), 75.9 (d), 78.9 (d), 128.2 (d), 128.3 (d), 128.6 (d), 135.9 (s), 157.4 (s, NHC=O), 170.1 (s, CH_3C=O), 171.1 (s, CH_3C=O) and 171.5 (s, CH_3C=O).

Oxazolidinone **18**.—The alcohol **16** (132 mg, 0.31 mmol) was dissolved in thionyl chloride (2 cm^3) and the solution heated to reflux for 3 h under an atmosphere of dry nitrogen. The reaction mixture was allowed to cool and the thionyl chloride removed under reduced pressure. Flash chromatography (ether) gave the *oxazolidinone* **18** as a white foam (74 mg, 82%), m.p. 40–41 °C (ether), $[\alpha]_D^{26}$ −24.1 (*c* 0.46 in $CHCl_3$) {lit.,[6] $[\alpha]_D$ −25 (*c* 0.41 in $CHCl_3$)}; ν_{max}(film)/cm^{-1} 1743, 1370 and 1227; δ_H(250 MHz; $CDCl_3$) 2.11 (3 H, s, OAC), 2.12 (3 H, s, OAc), 2.13 (3 H,

s, OAc), 2.63 (1 H, m, 5-H), 3.95 (1 H, dd, *J* 9.3 and 4.3, 2-H), 4.21 (2 H, d, *J* 5.2, CH_2OAc), 4.76 (1 H, dd, *J* 7.5 and 4.3, 3-H), 4.87 (1 H, dd, *J* 9.3 and 6.3, 1-H), 5.25 (1 H, dd, *J* 9.6 and 7.5, 4-H) and 5.82 (1 H, br s, NH); δ_C(22.5 MHz; $CDCl_3$) 20.7 (q, CH_3C=O), 48.3 (d, 6-C), 59.5 (d, 3a-C), 60.9 (t), 73.1 (d), 77.9 (d), 83.4 (d), 157.5 (s, NHC=O), 169.9 (s, CH_3C=O), 170.6 (s, CH_3C=O) and 171.2 (s, CH_3C=O) (Found: $M^+ + H$, 316.1041. $C_{13}H_{18}NO_8$ requires *M*, 316.1033).

Oxazolidinone **21**.—(*a*) trans-2-*Benzyloxycarbonylaminocyclopentanol*. To a rapidly stirred emulsion of *trans*-2-aminocyclopentanol[20] (610 mg, 6.05 mmol) in aqueous 2 mol dm^{-3} sodium hydroxide (20 cm^3) was added benzyl chloroformate (1.4 cm^3, 9.8 mmol). The reaction mixture was stirred vigorously at room temperature for 1 h and then poured into ether (20 cm^3). The aqueous phase was extracted with ether (3 × 20 cm^3) and the combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (10–20% ether in dichloromethane) gave the *title compound* as an oil which slowly crystallised at 0 °C (840 mg, 60%), m.p. 56–58 °C; ν_{max}(film)/cm^{-1} 3325, 2960, 2876, 1695 (C=O), 735 and 698; δ_H(250 MHz; $CDCl_3$) 1.37 (1 H, m), 1.59–2.16 (5 H, m), 3.70 (1 H, m, 2-H), 3.81 (1 H, br s, OH), 4.01 (1 H, m, 1-H), 4.96 (1 H, br s, NH), 5.09 (2 H, s, OCH_2Ph) and 7.35 (5 H, s, Ph); δ_C(22.5 MHz; $CDCl_3$) 20.2 (t), 29.6 (t), 31.7 (t), 59.9 (d, CHN), 66.4 (t), 77.9 (d, CHO), 127.6 (d, aryl CH), 128.1 (d, aryl CH), 136.2 (s, aryl C) and 156.8 (C=O) (Found: M^+, 235.1183. $C_{13}H_{17}NO_3$ requires *M*, 235.1208).

(*b*) *Oxazolidinone* **21**. The benzyl carbamate obtained in (*a*) above (640 mg, 2.72 mmol) was dissolved in thionyl chloride (5 cm^3) and heated to reflux under an atmosphere of dry nitrogen for 2 h. The reaction mixture was allowed to cool and the thionyl chloride removed under reduced pressure. Flash chromatography (20% ether in dichloromethane) gave the *title oxazolidinone* **21** as a white crystalline solid (320 mg, 92%), m.p. 87–90 °C; ν_{max}(KBr disc)/cm^{-1} 3254, 2970, 1739, 1246, 990 and 770; δ_H(250 MHz; $CDCl_3$) 1.49–1.87 (5 H, m), 2.11 (1 H, m), 4.28 (1 H, m, CHN), 5.06 (1 H, m, CHO) and 6.82 (1 H, br s, NH); δ_C(22.5 MHz; $CDCl_3$) 22.0, 33.9, 34.5, 56.8, 82.3 and 160.3 (Found: M^+, 127.0634. $C_6H_9NO_2$ requires *M*, 127.0633).

2-*Dimethylamino*-3a,4,5,6-*tetrahydrocyclopentoxazole* **23**.—To a solution of triethyloxonium tetrafluoroborate (132 mg, 0.69 mmol) in dichloromethane (2.8 cm^3) was added the oxazolidinone **21** (80 mg, 0.63 mmol). The solution was stirred under an atmosphere of nitrogen for 24 h. A solution of dimethylamine (100 mg, 2.2 mmol) in dichloromethane was added and the reaction mixture stirred for a further 2 h. The solution was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) and extracted with dichloromethane (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (20% ether in dichloromethane then acetone) gave the ethoxycyclopentoxazole **22** (36 mg, 37%), followed by the *title compound* **23** (61 mg, 63%) as an oil, ν_{max}(film)/cm^{-1} 2598, 1659, 1407 and 1185; δ_H(250 MHz; $CDCl_3$) 1.52–1.60 (4 H, m), 1.78 (1 H, m), 1.93 (1 H, m), 2.85 (6 H, s, NMe_2), 4.45 (1 H, m, CHN) and 4.94 (1 H, m, CHO); δ_C(22.5 MHz; $CDCl_3$) 21.7, 34.0, 34.6, 37.2, 69.2, 85.0 and 161.7 (Found: M^+, 154.1101. $C_8H_{14}N_2O$ requires *M*, 154.1106).

Triacetylallosamizoline **24**.—To the oxazolidinone **18** (23.2 mg, 0.074 mmol) was added a solution of triethyloxonium tetrafluoroborate (20 mg, 0.11 mmol) in dichloromethane (1 cm^3). The solution was stirred at room temperature overnight under an atmosphere of nitrogen. A solution of dimethylamine (65.4 mg, 1.4 mmol) in dichloromethane (1.4 cm^3) was added and the solution stirred for a further 24 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (ethyl acetate then acetone) gave *triacetylallosamizoline* **24** as a syrup (20 mg, 80%), $[\alpha]_D^{26}$ +28.8 (*c* 0.2 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1742, 1658, 1367 and 973; δ_H(250 MHz; $CDCl_3$) 2.02 (3 H, s, OAc), 2.06 (3 H, s, OAc), 2.11 (3 H, s, OAc), 2.61 (1 H, m, 5-H), 2.94 (6 H, s, NMe_2), 4.15 (1 H, dd, *J* 11.0 and 5.8, 6-H), 4.19 (1 H, dd, *J* 11.0 and 5.1, 6′-H), 4.45 (1 H, dd, *J* 8.6 and 3.7, 2-H), 4.85 (1 H, dd, *J* 8.6 and 5.1, 1-H), 5.05 (1 H, dd, *J* 7.8 and 5.7, 4-H) and 5.18 (1 H, dd, *J* 5.7 and 3.7, 3-H); δ_C(67.5 MHz; $CDCl_3$) 20.8 (q, CH_3C=O), 20.9 (q, CH_3C=O), 37.8 (q, NMe_2), 49.1 (d, 5-C), 61.5 (t, 6-C), 71.8 (d), 75.3 (d), 82.3 (d), 82.8 (d), 157.5 (s, C=N), 169.9 (s, CH_3C=O), 170.6 (s, CH_3C=O) and 171.2 (s, CH_3C=O) (Found: $M^+ - AcOH$, 282.1209. $C_{13}H_{18}N_2O_5$ requires *M*, 282.1216).

(−)-*Allosamizoline Hydrochloride* **1**.—To a solution of triacetylallosamizoline **24** (12.5 mg, 0.37 mmol) in methanol (1 cm^3) was added one drop from a solution of NaOMe, made by adding sodium (100 mg, 4.35 mmol) to methanol (10 cm^3). The reaction mixture was stirred at room temperature overnight under an atmosphere of nitrogen. Removal of solvent under reduced pressure and flash chromatography (1% triethylamine in methanol) of the residue afforded allosamizoline.

Methanolic HCl was added to the free base and the solvent removed under reduced pressure to give *allosamizoline hydrochloride* **1** (9.03 mg, 98%), $[\alpha]_D^{23}$ −21.7 (*c* 0.9 in H_2O); δ_H(400 MHz; D_2O, 298 K, DOH internal standard) 2.42 (1 H, m, 5-H), 3.08 (3 H, s, NMe), 3.10 (3 H, s, NMe), 3.73 (1 H, dd, *J* 7.3 and 11.5, 6-H), 3.83 (1 H, dd, *J* 7.0 and 8.6, 4-H), 3.90 (1 H, dd, *J* 4.5 and 11.5, 6′-H) 4.08 (1 H, dd, *J* 5.0 and 7.0, 3-H), 4.33 (1 H, dd, *J* 4.8 and 9.0, 2-H) and 5.36 (1 H, dd, *J* 9.0 and 5.3, 1-H); δ_C(100 MHz; D_2O, 3-trimethylsilylpropionic acid sodium salt external standard) 39.9 (q, NMe), 40.2 (q, NMe), 53.9 (d), 62.0 (t, 6-C), 66.2 (d), 77.5 (d), 84.2 (d), 89.3 (d) and 163.2 (s, N=CNMe$_2$).

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