Syntheses of the Fungicide/Insecticide Allosamidin and a Structural Isomer

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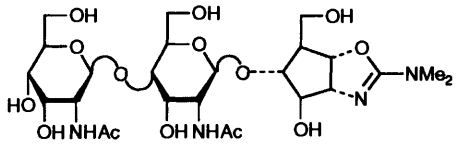
A synthesis of the naturally occurring inhibitor of chitin metabolism, allosamidin **1**, involves, as the key step, condensation between the allosamizoline derivative **39**, prepared following oxyamination of the cyclopentene **19**, and the disaccharide glycosylating agent **54** which was synthesised from 2-acetamido-2-deoxy-D-glucose. The structural isomer **59** of allosamidin is also reported. Brief biological test results obtained using isomers **1** and **59** are recorded.

Resistance to the dominant commercial insecticides—the synthetic pyrethroids—is increasing,[1] yet there is a paucity of reports of new classes of compounds for use in general insect control. Since chitin, the β-(1→4)-linked polymer of 2-acetamido-2-deoxy-D-glucopyranose, is partially degraded and reassembled during insect moulting, chitinases as well as chitin synthases are required by insects, and inhibitors of either of these enzyme types represent rational possibilities for control of insect development.

In the course of searches for such inhibitors, the chitotriose analogue allosamidin **1**,[2-4] in which the reducing terminal unit is adapted to a carbafuranose derivative and the other two units have undergone configurational inversion at C-3, was isolated from the mycelia of *Streptomyces* sp. 1713[5] and from the fermentation broth of sp. A82516.[6] It exhibits strong inhibition of chitinases of both insect and fungal origin, and prevents insect larval ecdysis *in vivo*.[2,5,7] It and some congeners are the only chitinase inhibitors reported thus far. We set out to prepare allosamidin by methods that were adaptable to the synthesis of structural analogues and now report the procedures developed.

Interest in compounds with these biological properties can be gauged by the observation that, since 1990, five synthetic routes to allosamizoline **2**—the cyclopentane-based component of allosamidin—have been described.[8-12] One of the reports[9] also describes the preparation of the complete trimer, and two[8,10] lead to other preparations of allosamidin.[13,14] In addition, reports of the preparation of allosamizoline analogues, notably cyclohexane-based compounds, have appeared[15] as have descriptions of the syntheses of carbadisaccharides which are glycosylated cyclohexane derivatives akin to glycosylated allosamizolines.[16] Feeding experiments with labelled D-glucose and 2-amino-2-deoxy-D-glucose have shown that both carbohydrate rings and the allosamizoline ring are derived biosynthetically from the latter sugar.[17]

Two of the syntheses of allosamizoline were based on the cyclopentadiene-derived 4-benzyloxymethyl-3,5-dihydroxycyclopentene **3**, the first[8] giving the product in racemic form by way of a cyclopentene oxazolidinone and a derived epoxide, and the second[9] following a similar route but giving enantiomerically pure product. In this latter case the diacetate of compound **3** was converted into an enantiomerically pure monoacetate by selective, enzymic partial hydrolysis. The other three routes to the required cyclopentane derivative began from 2-amino-2-deoxy-D-glucose, the first[10] using a carbocyclisation conversion of a 6-deoxy-5-enopyranoside derivative to give the corresponding cyclohexenone by use of a mercury(II) salt,[18] and then ring contracting the derived inosamine tosyl derivative **4**. The second[11] relied, in the critical cyclopentane-forming step, on the intramolecular 1,3-dipolar cycloaddition of the nitrile oxide **5**, and the third[12] on cyclisation of the radical **6**.



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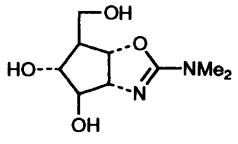

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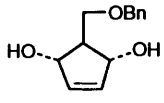

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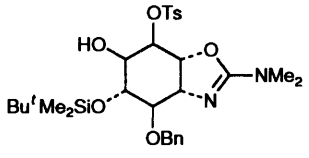

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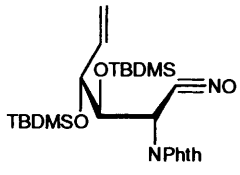
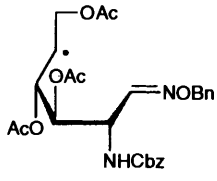


5 TBDMS = $SiMe_2Bu^t$



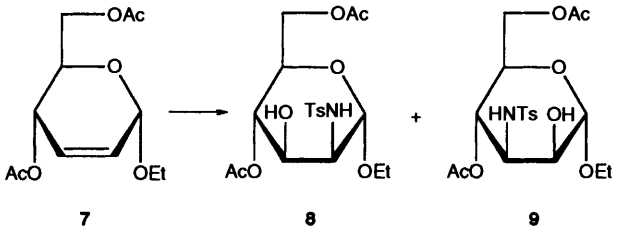
6 Cbz = CO_2CH_2Ph

Results and Discussion

In this paper we describe the synthesis of allosamidin, and an isomer with the disaccharide linked to the alternative secondary hydroxy group of allosamizoline, by coupling of a disaccharide glycosyl donor with a partially protected allosamizoline acceptor, a route akin to that employed by the Trost and Vasella groups.[13] The disaccharide glycosyl trichloroacetimidate **54** was, however, prepared by two alternative, somewhat modified procedures, and the allosamizoline-based diol **39** was obtained in enantiomerically pure form by oxyamination of the glucose-derived alkene **19** (see Scheme 2) rather than as the racemate which was used in the earlier work.[13] This approach also affords potential access to isomers and analogues of allosamidin having the carbohydrate moieties linked to the isomer of the acceptor **39** with the two rings fused such that the nitrogen atom and the carbon substituent are vicinal.

Having previously developed a route to the enantiomerically pure cyclopentene **19** from methyl α-D-glucopyranoside[19] we

were attracted to the possible application of it and of related compounds to the synthesis of suitably substituted derivatives of allosamizoline, and investigated in this context the Sharpless osmium-catalysed oxyamination reaction[20,21] which is known to yield, as required for allosamidin synthesis, 1,2-*cis*-hydroxyamines from the sterically accessible face of alkenes. Previously, in the carbohydrate field, Dyong *et al.*[22] applied a combination of Chloramine-T, silver nitrate and osmium tetraoxide to convert ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **7** into the 2-deoxy-2-tosylamino- and 3-deoxy-3-tosylamino-α-D-mannopyranosides **8** and **9** in 20 and 45% yield, respectively (Scheme 1), confirming that the



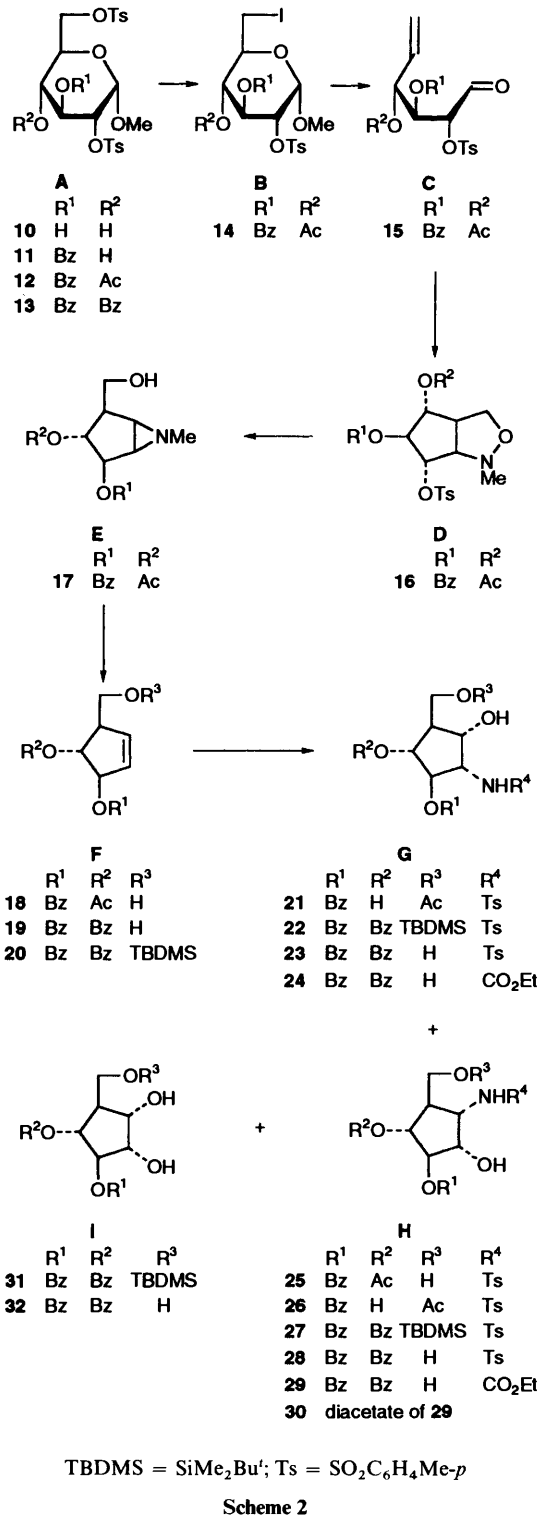
7 **8** **9**

Scheme 1

reaction gives products having a *trans*-relationship between the introduced *cis*-functional groups and the allylic ring substituents but with no great regioselectivity. Using the analogous unsaturated methyl glycoside diacetate, Heyns and Feldmann isolated the methyl 2-deoxy-2-tosylamino- and 3-deoxy-3-tosylamino-mannopyranoside triacetates, each in 40% yield, following acetylation of the initial reaction products.[23] The strategy utilised in the present work involves the conversion of methyl glucoside 2,6-ditosylates [2,6-bis(toluene-*p*-sulfonates)] of set **A** into 6-deoxy-6-iodo-2-*O*-(toluene-*p*-sulfonyl)-D-glucopyranosides **B**, then into enals **C**, isoxazolidines **D**, aziridines **E**, cyclopentenes **F** and into the required compounds of the **G** set (Scheme 2). During the last step some products belonging to the **H** and **I** sets were expected. It is noteworthy that an enantioselective oxyamination procedure, published after the work here reported was completed,[24] could have important relevance to the regioselectivities encountered in the **F**→**G**, **H** step of this sequence.

Because synthesis of allosamidin by the route selected involves the glycosylation of an allosamizoline derivative with an unsubstituted hydroxy group at the carbon atom derived from C-4 of the initial glucoside, a methyl glucoside ditosylate of series **A** was sought with selectively removable substituents at O-3 and O-4 as starting material. To this end methyl 2,6-bis-*O*-(toluene-*p*-sulfonyl)-α-D-glucopyranoside **10**[18] was selectively benzoylated at O-3 to give compound **11** and the product was acetylated to give crystalline compound **12** (47% from the ditosyl substrate **10**) which, on treatment with sodium iodide in refluxing acetic anhydride, afforded iodide **14** (83%).

Treatment of the iodide with zinc in ethanol gave enal **15**, the reaction of which with *N*-methylhydroxylamine then afforded the isoxazolidine **16** (57% from iodide **14**). Reduction with hydrogen over Raney nickel gave the aziridine **17**, and peracid oxidation resulted in the required cyclopentene **18**. Oxyamination using Chloramine-T and catalytic proportions of osmium tetraoxide[20,21] proceeded but, instead of two tosylamino products, three were identified by ^{1}H NMR means: (i) the expected adduct **25** (14%), with the nitrogen-bonded substituent adjacent to the hydroxymethyl group, and (ii) both products of oxyamination of the alkene which had also undergone migration of the acetyl group from the secondary to the primary site, *i.e.* compounds **21** (9%) and **26** (12%). Such migrations are commonly found with hydroxyacetates of this kind[25] and have been observed previously during oxyamination reactions.[23] In



A

	R^1	R^2
10	H	H
11	Bz	H
12	Bz	Ac
13	Bz	Bz

B

	R^1	R^2
14	Bz	Ac

C

	R^1	R^2
15	Bz	Ac

D

	R^1	R^2
16	Bz	Ac

E

	R^1	R^2
17	Bz	Ac

F

	R^1	R^2	R^3
18	Bz	Ac	H
19	Bz	Bz	H
20	Bz	Bz	TBDMS

G

	R^1	R^2	R^3	R^4
21	Bz	H	Ac	Ts
22	Bz	Bz	TBDMS	Ts
23	Bz	Bz	H	Ts
24	Bz	Bz	H	CO_2Et

I

	R^1	R^2	R^3
31	Bz	Bz	TBDMS
32	Bz	Bz	H

H

	R^1	R^2	R^3	R^4
25	Bz	Ac	H	Ts
26	Bz	H	Ac	Ts
27	Bz	Bz	TBDMS	Ts
28	Bz	Bz	H	Ts
29	Bz	Bz	H	CO_2Et
30	diacetate of **29**			

TBDMS = $SiMe_2Bu^t$; Ts = $SO_2C_6H_4Me$-*p*

Scheme 2

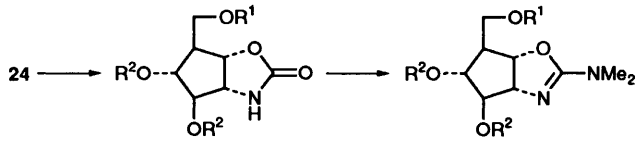
the present case, although they were ideally suited for glycosylation, the two products of acetyl migration were not separable and this critical factor and the unfavourable ratio of regioisomers led to the pursuit of other possibilities.

Oxyamination, by use of Chloramine-T, of the *tert*-butyldimethylsilyl ether **20** of the alkene **19**, which has previously been made[19] from the ditosyl compound **13** by the route indicated in Scheme 2, gave the expected products **22** and **27** in the ratio 1:3.7 as well as some of the analogous 1,2-diol **31** which is expected as a by-product of the reaction.[20] Again, the required compound **22** was not separable on chromatograms from its regioisomer **27**.

Under the same conditions the dibenzoylated alkene **19** gave adducts **23** and **28** in disadvantageous proportions (1:6.6), but now they were readily separable on TLC plates, suggesting that focus should be on products with free primary hydroxy groups. Furthermore, in the expectation that the ratio of oxyamination products would be more in favour of the regioisomers of the **G** set (as required for allosamizoline) when the nitrogen function of the amine used in the oxyamination reagent was less space-demanding than the tosyl group of Chloramine-T, and recognising that the target molecule contained a heterocyclic ring that could be made directly from an α-hydroxy carbamate ester, we next applied the *N*-chloro-*N*-metallocarbamate modification[26] of the Sharpless reaction. By use of the heterogeneous system sodio ethyl *N*-chlorocarbamate and silver nitrate in aqueous acetonitrile to which catalytic amounts of osmium tetraoxide were added in *tert*-butyl alcohol, the readily separable oxyamination adducts **29** (25%) and **24** (29%), together with the diol **32** (19%), were obtained from alkene **19**. Use of the homogeneous system mercury(II) trifluoroacetate and the chlorocarbamate in acetonitrile without added water, however, gave more satisfactory results: compounds **29** (contaminated with ethyl carbamate and acetylated to give compound **30**) and **24** were obtained in 20 and 40% respectively, with only trace proportions of the diol **32**.

On treatment with sodium methoxide in refluxing methanol the regioisomer **24**, required for allosamidin synthesis, gave the triol **33** and hence the known triacetate **34**,[11,12] which was converted (trimethyloxonium tetrafluoroboranuide in dichloromethane followed by dimethylamine)[12] into the previously reported triacetylallosamizoline **37**[3,12] (Scheme 3). Removal of the acetyl groups afforded the previously unreported crystalline allosamizoline **2** which, on treatment with hydrogen chloride, gave the known hydrochloride[3,12] to confirm the structure of oxyamination product **24**.

In the course of attempted selective benzylation of compound **24** at the primary alcohol site [which caused appreciable difficulty (see ref. 14)] it was discovered that treatment in refluxing



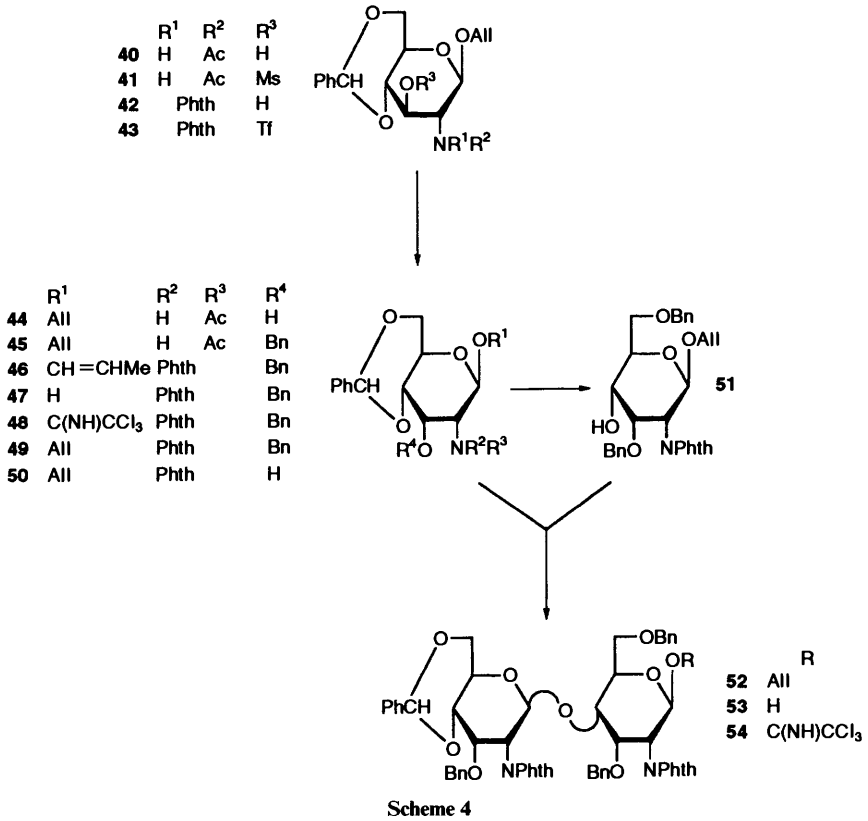
	R^1	R^2
33	H	H
34	Ac	Ac
35	H	Bz
36	Bn	Bz

	R^1	R^2
2	H	H
37	Ac	Ac
38	Bn	Bz
39	Bn	H

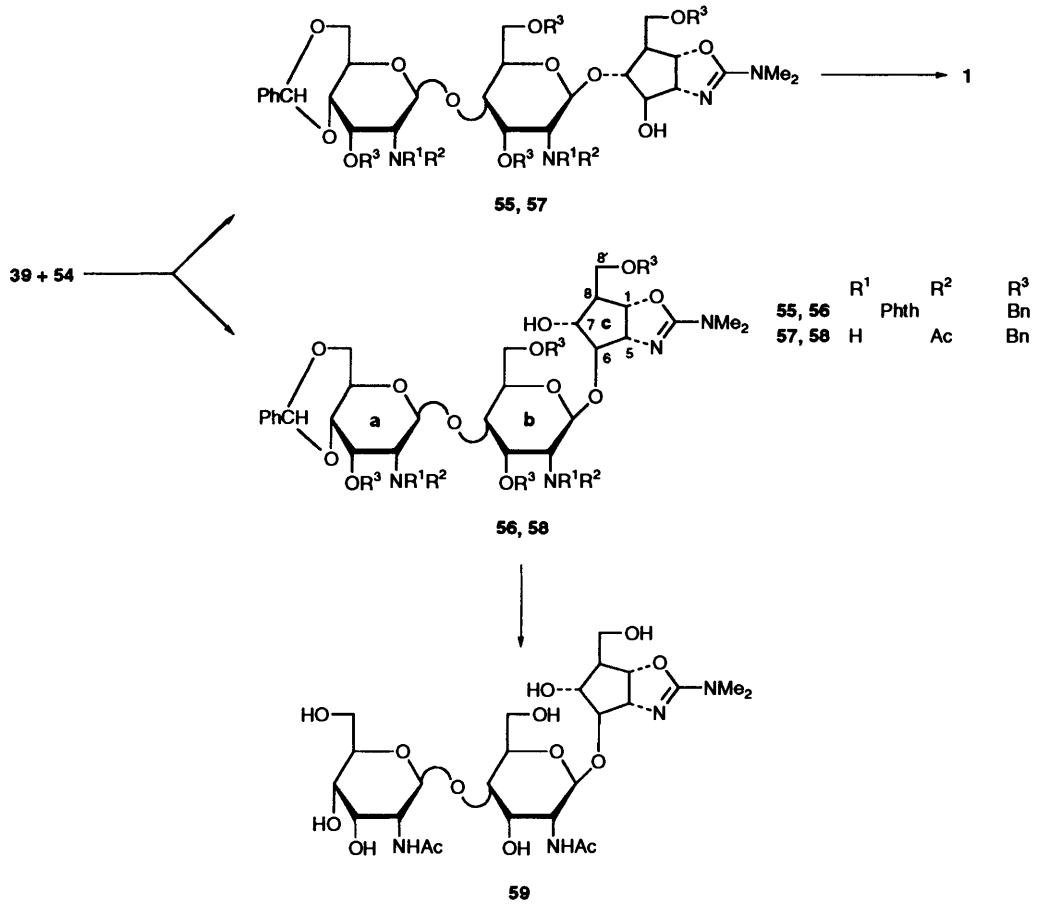
Scheme 3

toluene with bis(tributyltin) oxide and removal of ethanol promoted cyclisation to the cyclic carbamate **35**, presumably following activation of the hydroxy group.[27] The cyclic carbamate underwent benzylation [benzyl trichloroacetimidate, trifluoromethanesulfonic acid (TFSA) in dichloromethane–cyclohexane][28] to give compound **36** (70%). Conversion of this oxazolidinone into the *N*,*N*-dimethylamino compound **38** followed by debenzoylation then afforded the diol **39** (71%) which is the appropriate enantiomer of the racemic compound used in the Vasella, Trost synthesis of allosamidin.[13]

The method chosen to make the disaccharide component of the target compound was similar to that employed by Maloisel and Vasella[29] except that allyl β-glycosides were used throughout (rather than α-anomers) as precursors of glycosyl trichloroacetimidates which, as in the previous work,[13] were selected as glycosyl donors (Scheme 4). Thus, the known allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside **40**[30] was mesylated to give compound **41** which, on solvolysis in wet 2-methoxyethanol, gave the 2-acetamido-2-deoxy-D-allose derivative **44** in 91% yield. Benzylation of this alcohol afforded compound **45**, which on N-deacetylation with potassium hydroxide in methanol without added water at 125 °C for 48 h followed by N-phthaloylation gave the propenyl glycoside **46** in 71% yield. The allyl group had thus undergone convenient isomerisation and the product was readily converted into the



Scheme 4



Scheme 5

free sugar **47** and hence the glycosyl donor **48**. By this means it is possible to avoid the difficulties experienced by Maloisel and Vasella[29] who found the α-anomer of compound **45** to be very resistant to N-deacetylation and the C-3 hydroxy group of allyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-α-D-allopyranoside resistant to benzylation.

The glycosyl acceptor **51** was obtained by N-deacetylation of compound **45** with potassium hydroxide in methanol containing 20% water for 5 days at 125 °C under which circumstances, remarkably, no rearrangement of the allyl group occurred. N-Phthaloylation gave the fully substituted product **49** (61%), which was then treated with sodium cyanoboranuide and hydrogen chloride to reduce selectively the benzylidene acetal. An alternative route to compound **49** and thus to both the precursor **46** of the glycosylating reagent **48** and the glycosyl acceptor **51** involved the triflate **43** of the known 2-phthalimidoglucoside **42**[31] which, on treatment with tetrabutylammonium nitrite in dimethylformamide (DMF) at 55 °C,[32] underwent displacement of the sulfonyloxy group with inversion of configuration to give the alloside **50** in 62% yield and hence the O-benzylated derivative **49**. While this approach avoided the time-consuming N-deacetylation of compound **45** and gave access to both the glycosyl donor **48** and glycosyl acceptor **51**, it has the disadvantage of requiring the use of an expensive catalyst to isomerise the allyl group of compound **49** *en route* to the acetimidate **48**.

Coupling of the acceptor **51** with the trichloroacetimidate **48** gave the disaccharide allyl glycoside **52** (85%), which on deallylation led to the same free sugar **53** and disaccharide glycosylating agent **54** as were used in the previous work.[13]

Condensation of benzylallosamizoline **39** with the crystalline dimeric glycosylating agent **54** on the 1.2 mmol scale in dichloromethane in the presence of trimethylsilyl triflate (1 mol equiv.) occurred with good selectivity at the required position, the β-linked products **55** and **56** being formed in the ratio 5:1 in 68% yield (Scheme 5). These findings follow closely those of Maloisel *et al.*[13] who used similar conditions. When the reaction was carried out on the 0.25 mmol scale with 0.3 mol equiv. of the triflate much poorer selectivity was obtained. The mixture of products **55** and **56** was readily characterised by use of the detailed NMR data provided by the Vasella, Trost groups.[13]

Dephthaloylation of compounds **55**, **56** was effected by use of aq. methylamine, the mixed diamines were purified chromatographically prior to acetylation and separation to give the known derivative **57** in 79% and its isomer **58** in 18% yield, respectively. Hydrogenolysis of these compounds in methanol–acetic acid furnished allosamidin **1** and its isomer **59** in nearly quantitative yields.

Results from biological tests on allosamidin **1** were consistent with published observations.[5,7] Although inhibition of chitinase from *Streptomyces griseus* was weak, fourth instar larvae of *Heliothis virescens* all died within 5 days of being injected with 0.5 mm^3 of a 10% aqueous solution of **1**. Analogue **59**, on the other hand, was a considerably weaker inhibitor of the microbial chitinase, and although 33% of the insect larvae injected remained smaller than average size, no deaths occurred after 5 days.

Experimental

NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal reference by use of a Bruker AC300E instrument unless otherwise stated. For COSY

Table 1 ^{1}H NMR chemical shifts for cyclopentane derivatives[a]

Compound	1-H	2-H	3-H	4-H	4'-H	4'-H'	5-H	5'-H	5'-H'
2[b]	4.82	4.01	3.77	3.67			2.14	3.89	3.73
2·HCl salt[b]	5.37	4.33	4.08	3.83			2.43	3.90	3.74
18	5.96	5.96	5.96	5.23			2.86	3.80	3.69
20	6.08	5.98	6.08	5.57			3.00	3.90	3.82
21	4.0	3.69	5.32	3.9			2.38	4.2	4.2
22	4.17	3.49	5.83	5.50			2.30	3.8	4.0
23	4.31	3.8	5.84	5.40			2.37	3.91	3.87
24	4.32	4.20	5.89	5.42			2.34	3.94	3.86
31	4.17	4.25	5.54	5.60			2.42	3.89	3.96
32	4.2	4.2	5.53	5.45			2.41	3.92	3.84
33	5.43	4.44	4.64	4.60			2.85	4.32	4.32
34	4.87	3.95	4.77	5.24			2.63	4.21	4.21
35	5.12	4.09	5.21	5.66			2.54	3.90	3.80
36	5.10	4.09	5.10	5.89			2.76	3.77	3.64
37	4.76	4.36	5.13	5.04			2.56	4.21	4.17
38	5.46	4.63	5.53	5.46			2.85	3.71	3.61
39	4.72	4.02	3.84	3.71			2.13	3.7	3.7
25	3.7	4.98	5.24	2.29	3.67	3.55	3.7		
26	4.0	4.93	3.9	2.38	4.2	4.2	3.55		
27	3.94	5.23	5.55	2.53	3.79	3.79	3.71		
28	3.8	5.17	5.50	2.40	3.8	3.8	3.8		
29	4.2	5.17	5.60	2.43	4.1	4.2	4.2		
30	5.32	5.50	5.45	2.60	4.38	4.29	4.50		

[a] ***N.B.*** For the purposes of this Table only, all compounds are numbered as cyclopentanol derivatives. The first set have the OH-bearing C-1 α-related to the branch position which becomes C-5; the second set have the OH-bearing C-1 β-related to the branch position which becomes C-4. Other resonances, consistent with the assigned structures, were observed in all cases. [b] Measured in D_2O with respect to sodium 4,4-dimethyl-4-silapentanesulfonate at 500 MHz.

Table 2 ^{1}H NMR coupling constants (J/Hz) for cyclopentane derivatives[a]

Compound	$J_{1,2}$	$J_{1,5}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,4'}$	$J_{4,4''}$	$J_{5,5'}$	$J_{5,5''}$	$J_{5,5''}$
2[b]	9.2	6.1	5.5	7.9	9.7			4.3	7.3	11.6
2·HCl salt[b]	9.2	5.2	4.9	6.8	8.2			4.3	7.3	11.6
18	0	0.7	0	2.6	2.6			4.5	7.3	
20	4.6		1.8	3.2	3.2			5.4	5.4	
21	5.8		9.2	6.6	5.8					
22	4.4	< 1	10.0	6.8	5.0					
23	5.6	2.9	9.6	7.3	6.9			4.5	5.1	
24	5.4	3.4	9.3	7.1	6.5			4.8	5.4	
31	4.5	4.5	6.5	5.5	6.5			3.4	4.4	
32			4.0	6.3	6.3			4.1	4.7	
33	9	6	5	7.5	7.5			5	5	
34	6.2	4.2	7.3	9.3				5.3	5.3	
35	9.4	7.1	4.5	8.3	10.5					
36	9.2		4.3	7.5	9.1					
37	8.5	4.9	3.6	5.6	7.7			5.8	6.6	11.5
38	7.9	2.7	1.0	3.5	3.5			5.9	7.9	9.5
39	9.1	6.4	5.1	7.8	9.7					
25	< 1		5.8	9.5	9	2.6	2.8			
26	1.8		4.6	9.2						
27	3.6	6.0	4.9	7.8						
28	< 1		5.9	9.5						
29	< 1		5.1	9.7						
30	2.1	5.6		9	9	4.2	5.0			

[a] ***N.B.*** For the purposes of this Table only, all compounds are numbered as cyclopentanol derivatives. The first set have the OH-bearing C-1 α-related to the branch position which becomes C-5; the second set have the OH-bearing C-1 β-related to the branch position which becomes C-4. [b] As in Table 1.

experiments standard Bruker-supplied pulse sequences were used with results displayed in magnitude mode. All signal assignments were made by ^{1}H–^{1}H and ^{1}H–^{13}C COSY methods. NMR data are given in Tables 1–6. J-Values are given in Hz.

Optical rotations were, unless otherwise stated, determined for chloroform solutions (0.2–1.6 g/100 cm^3) with a Perkin-Elmer 241 automatic polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. M.p.s were measured by use of a Reichert Jung Thermovar hot-stage apparatus and were corrected by use of reference compounds.

For column chromatography, silica gel (0.063–0.04 mm) was used and the columns were eluted in the flash mode.[33] Radial chromatography was performed on a Harrison Research Chromatotron model 7924T using silica gel 60 PF_{254} (with $CaSO_4$ binder)-coated plates.

Osmium tetraoxide solutions were prepared by dissolution of the reagent (freshly opened, 0.5 g for solution A; 0.1 g for

solution B) in *tert*-butyl alcohol (freshly distilled, 19.9 cm^3) containing *tert*-butyl hydroperoxide (0.1 cm^3, solution A; 0.6 cm^3, solution B). Light petroleum refers to the fraction boiling in the range 60–80 °C.

Methyl 4-O-*Acetyl*-3-O-*benzoyl*-2,6-*di*-O-(*toluene*-p-*sulfonyl*)-α-D-*glucopyranoside* **12**.—Selective sulfonylation of methyl α-D-glucopyranoside gave a syrupy ditosyl derivative[18] which was purified by flash chromatography. A stirred sample (3.29 g) in dichloromethane (140 cm^3) and pyridine (5.6 cm^3) was treated, under nitrogen, with benzoyl chloride (0.49 g, 0.5 mol equiv.) at 0 °C and, after 7 h at this temperature, with further reagent (1.22 g, 1.25 mol equiv.). The solution was allowed to come to 20 °C and was stirred for a further 30 h, when all starting material had reacted. Methanol (10 cm^3) was added and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane and resolved on a column of silica gel to give methyl 3-*O*-benzoyl-2,6-di-*O*-tosyl-α-D-glucopyranoside **11** (2.18 g, 55%); δ_H 2.25 and 2.42 (6 H, 2 s, Ar*Me*), 3.32 (3 H, s, OMe), 3.69 (1 H, t, $J_{3,4} = J_{4,5} = 9.2$, 4-H), 3.82 (1 H, dd, $J_{5,6}$ 2.1, $J_{5,6'}$ 3.9, 5-H), 4.22 (1 H, dd, 6-H), 4.31 (1 H, dd, 6-H'), 4.49 (1 H, dd, $J_{1,2}$ 3.3, $J_{2,3}$ 9.9, 2-H), 4.84 (1 H, d, 1-H), 5.47 (1 H, t, 3-H) and 7.0–7.8 (13 H, ArH); δ_C 21.5 and 21.6 (Ar*Me*), 55.0 (OMe), 68.4 (C-6), 69.0 (C-4), 69.3 (C-5), 72.7 (C-3), 76.2 (C-2), 97.5 (C-1), 127–145 (Ar) and 166.5 (C=O). The known methyl 3,4-di-*O*-benzoyl-2,6-di-*O*-tosyl-α-D-glucopyranoside **13**[18] (1.73 g, 37%) was also obtained.

A solution of the monobenzoate **11** (2.18 g), in pyridine (20 cm^3), was treated with acetic anhydride (10 cm^3) at 20 °C for 1 h. The mixture was poured onto ice and the solid was recrystallised from methanol to give the *monoacetate-monobenzoate* **12** (2.33 g, 86%), m.p. 138–142 °C; $[\alpha]_D$ +101 (Found: C, 55.6; H, 5.1. $C_{30}H_{32}O_{12}S_2$ requires C, 55.5; H, 5.0%); δ_H 1.79 (3 H, s, Ac), 2.20 and 2.45 (6 H, 2 s, Ar*Me*), 3.41 (3 H, s, OMe), 4.0–4.15 (3 H, m, 5-H, 6-H_2), 4.45 (1 H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 10.0, 2-H), 4.96 (1 H, d, 1-H), 5.05 (1 H, t, $J_{3,4} = J_{4,5} = 9.6$, 4-H), 5.64 (1 H, t, 3-H) and 7.0–7.8 (13 H, ArH); δ_C 20.3 (*Me*CO), 21.6 and 21.7 (Ar*Me*), 56.1 (OMe), 67.0, 67.5 and 68.3 (C-6, -5, -4), 69.9 (C-3), 76.2 (C-2), 97.7 (C-1), 127–145 (Ar) and 165.0 and 169.2 (C=O).

Methyl 4-O-*Acetyl*-3-O-*benzoyl*-6-*deoxy*-6-*iodo*-2-O-(*toluene*-p-*sulfonyl*)-α-D-*glucopyranoside* **14**.—The mixed ester **12** (1.8 g) was heated with sodium iodide (2.0 g) in refluxing acetic anhydride (36 cm^3) for 1 h. The mixture was filtered, the solvent was removed, and the residue was dissolved in dichloromethane (75 cm^3). The solution was extracted with saturated aq. sodium thiosulfate (2 × 30 cm^3), washed with water, and dried ($MgSO_4$). Removal of the solvent and recrystallisation of the residue from methanol gave the *iodide* **14** (1.39 g, 83%), m.p. 170–171 °C; $[\alpha]_D$ +107 (Found: C, 45.9; H, 4.3. $C_{23}H_{25}IO_9S$ requires C, 45.7; H, 4.2%); δ_H 1.88 and 2.21 (6 H, 2 s, Ar*Me*), 3.125 (1 H, dd, $J_{5,6}$ 8.0, $J_{6,6'}$ 10.9, 6-H), 3.30 (1 H, dd, $J_{5,6'}$ 2.6, 6-H'), 3.52 (3 H, s, OMe), 3.84 (1 H, ddd, $J_{4,5}$ 9.6, 5-H), 4.53 (1 H, dd, $J_{1,2}$ 3.7, $J_{2,3}$ 10.0, 2-H), 4.95 (1 H, t, $J_{3,4}$ 9.6, 4-H), 5.03 (1 H, d, 1-H), 5.69 (1 H, t, 3-H) and 7.0–7.8 (9 H, ArH); δ_C 3.3 (C-6), 20.5 and 21.5 (Ar*Me*), 56.2 (C-5), 68.6, 69.4 and 72.2 (C-4, -3, -2), 97.7 (C-1), 127–145 (Ar) and 165.0 and 169.4 (C=O).

(1R,5R)-6-exo-*Acetoxy*-7-endo-*benzoyloxy*-N-*methyl*-8-exo-(*toluene*-p-*sulfonyloxy*)-3-*oxa*-2-*azabicyclo*[3.3.0]*octane* **16**.—The iodide **14** (1.39 g) was heated in refluxing ethanol (45 cm^3)

Table 3 ^{13}C NMR chemical shifts for cyclopentane derivatives[a]

Compound	C-1	C-2	C-3	C-4	C-4'	C-5	C-5'
2[b]	85.3	73.9	87.1	77.6		54.4	63.2
2·HCl salt[b]	89.6	66.7	84.6	77.8		54.3	62.3
18	127.5[c]	135.7[c]	83.9	81.1		54.8	64.1
20	128.8[c]	137.0[c]	84.5	80.4		54.0	64.1
21	74.3	63.4	83.1	74.5		50.9	61.0
22	73.9	60.6	79.8	75.9		52.1	62.9
23	71.5	59.2	78.8	75.1		52.2	61.6
24	71.1	57.1	79.3	75.9		52.7	61.7
31	73.5	75.6	85.1	76.2		51.2	62.5
32	71.1	74.5	84.2	75.0		51.0	60.7
33	79.3	62.0	85.3	76.7		57.6	60.2
34	75.3	60.8	83.4	73.1		48.3	59.5
35	76.2	59.2	84.2	72.3		50.8	57.9
36	77.7	59.8	85.2	73.5		49.3	65.9
37	82.0	72.5	83.1	75.5		49.2	61.6
38	84.6	74.4	83.8	78.0		51.8	67.7
39	82.6	72.4	84.7	74.1		50.2	68.7
25	72.7	84.7	73.1	48.6	57.8	52.7	
26	73.4	86.6	74.3	47.7	58.7	54.0	
27	73.4	87.5	74.9	49.5	59.7	54.6	
28	72.9	84.7	73.7	48.9	57.8	52.8	
29	74.2	85.1	74.5	49.3	61.6	50.5	
30	75.5	79.4	77.2	51.8	61.5	47.2	

[a] ***N.B.*** For the purposes of this Table only, all compounds are numbered as cyclopentanol derivatives. The first set have the OH-bearing C-1 α-related to the branch position which becomes C-5; the second set have the OH-bearing C-1 β-related to the branch position which becomes C-4. Other resonances, consistent with the assigned structures, were observed in all cases. [b] Measured in D_2O with respect to sodium 4,4-dimethyl-4-silapentanesulfonate at 500 MHz. [c] Might be interchanged.

Table 4 ^1H NMR chemical shifts for pyranoid derivatives[a]

Compound	1-H	2-H	3-H	4-H	5-H	6-H	6-H'	1'-H		2'-H	3'-H	
40[b]	4.49	3.8	3.8	3.43	3.4	4.2	3.73	4.00	4.19	5.82	5.12	5.24
41[b]	4.73	3.8	4.80	3.8	3.5	4.2	3.8	4.04	4.2	5.84	5.14	5.25
43	5.38	4.55	5.73	3.93	3.71	4.46	3.88	4.04	4.28	5.76	5.05	5.13
44[b]	4.69	3.8	3.96	3.63	3.8	4.2	3.70	4.02	4.20	5.85	5.12	5.23
45	4.67	4.1	4.05	3.67	4.1	4.36	3.75	4.01	4.2	5.80	5.12	5.23
46	6.31	4.2	4.25	3.86	4.3	4.44	3.84	6.22		4.53	1.41	
47	6.40	4.07	4.23	3.84	4.3	4.41	3.80					
49	6.11	4.1	4.23	3.82	4.1	4.42	3.82	4.1	4.2	5.84	5.09	5.19
50[c]	5.99	4.4	4.4	3.78	4.22	4.32	3.86	4.12	4.33	5.80	5.08	5.17
51	5.93	4.05	4.15	3.85	4.00	3.8	3.8	4.13	4.33	5.85	5.07	5.17
52[d]	5.87	3.99	4.3	3.95	4.1	3.5	3.5	4.1	4.3	5.85	5.02	5.12
52[e]	6.27	4.1	4.19	3.82	4.3	4.48	3.79					
53[d]	6.11	3.85	4.25	3.88	4.0	3.5	3.5					
53[e]	6.18	4.1	4.1	3.74	4.23	4.4	3.71					

[a] Other resonances consistent with the assigned structures were observed in all cases. [b] Measured in deuteriated Me_2SO. [c] Measured at 500 MHz. [d] Central ring resonances. [e] Terminal carbohydrate ring resonances.

Table 5 ^{1}H NMR coupling constants (J/Hz) for pyranoid derivatives

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{NH,2}$
40[a]	8.0	9	9.2	9.2		10.0	10.0	8.4
41[a]	8.2	9.7	9.7	9.6	4.8	9.6		9.0
43	8.2	10.0	9.6	9.4	4.9	10.3	10.3	
44[a]	8.7	1.9	1.9	9.3	4.9	10.1	10.1	8.7
45	8.5	1.9	1.9	9.4	4.9	10.3	10.3	9.1
46	8.7	2.8	2.1	9.4	5.1	10.2	10.2	
47	8.7	2.7	2.1	9.7	5.1	10.2	10.2	
49	8.8	2.9	2.4	9.2	5.2	10.3	10.3	
50[b]	8.8		2.7	9.5	4.9	10.3	10.3	
51	8.7	2.6	2.7	9.8	4.7			
52[c]	8.7	2.6	2.4	10.0				
52[d]	8.4		2.1	9.4	5.6	10.2	10.2	
53[c]	8.5	2.5	2.4	9.3				
53[d]	8.4	2.1	9.5	5.0	5.1	10.2		

[a] Measured in deuteriated Me_2SO. [b] Measured at 500 MHz. [c] Central ring data. [d] Terminal carbohydrate ring data.

Table 6 ^{13}C NMR chemical shifts for pyranoid derivatives[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′
40[b]	102.3	57.1	71.5	82.3	67.1	69.0	70.3	136.6	117.5
41[b]	101.7	55.1	81.1	79.4	66.5	68.9	70.7	135.6	117.9
43	97.8	55.0	82.4	78.8	65.7	68.5	70.7	133.0	118.3
44[b]	100.3	54.1	68.8	79.9	64.2	69.7	70.5	136.1	117.9
45	99.8	52.2	76.0	80.2	63.9	69.3	70.0	134.1	117.1
46	96.8	56.3	73.9	79.7	64.4	69.0	142.9	104.3	9.2
47	91.3	58.1	74.0	79.9	64.4	69.1			
49	97.0	56.8	74.1	80.1	64.1	69.3	70.9	134.0	117.4
50	96.4	56.5	69.5	79.1	63.8	69.2	70.7	134.2	117.5
51	96.4	56.5	77.5	70.8	72.8	70.7	70.7	134.3	117.4
52[c]	96.2	56.7	76.8	77.0	72.5	69.9	70.5	134.4	117.1
52[d]	98.0	56.9	74.2	80.0	64.0	69.2			
53[c]	90.6	57.9	76.6	76.9	72.4	70.2			
53[d]	98.1	56.9	74.2	80.0	64.1	69.2			

[a] Other resonances, consistent with the assigned structures, were observed in all cases. [b] Measured in deuteriated Me_2SO. [c] Central ring references. [d] Terminal carbohydrate ring reference.

in the presence of zinc powder (1.22 g) for 40 min. The mixture was filtered through Celite, the Celite was washed (dichloromethane, 10 cm^3) and the filtrate and washings were evaporated to give enal **15**, which was dissolved in ethanol–pyridine (14 cm^3/5.5 cm^3). *N*-Methylhydroxylamine hydrochloride (0.23 g, 1.0 mol equiv.) was added and the mixture was heated at 45 °C for 1.6 h. The majority of the solvent was evaporated off and the solution was poured into ice–water to give a sticky solid. Filtration, and crystallisation from methanol, gave the *isoxazolidine* **16** (0.62 g, 57%), m.p. 145–147 °C; $[\alpha]_D$ +37.4 (Found: C, 58.0; H, 5.8; N, 3.1. $C_{23}H_{25}NO_8S$ requires C, 58.1; H, 5.3; N, 3.0%); δ_H 2.20 (3 H, s, Ac), 2.21 (3 H, s, Ar*Me*), 2.61 (3 H, s, NMe), 3.11 (1 H, dddd, $J_{1,5}$ 9.6, $J_{4,5}$ 7.2, $J_{4',5}$ 3.2, $J_{5,6}$ 6.8, 5-H), 3.56 (1 H, dd, $J_{1,8}$ 5.2, 1-H), 4.02 (1 H, dd, $J_{4,4'}$ 9.9, 4-H′), 4.09 (1 H, dd, 4-H), 4.90 (1 H, dd, $J_{7,8}$ 8.3, 8-H), 4.95 (1 H, dd, $J_{6,7}$ 8.2, 6-H), 5.68 (1 H, t, 7-H) and 7.0–7.8 (9 H, ArH); δ_C 20.7 (*Me*CO), 21.5 (Ar*Me*), 43.4 (C-5), 50.1 (NMe), 69.4 (C-4), 72.7, 77.7, 78.0 and 84.0 (C-6, -7, -8, -9), 128–145 (Ar) and 164.9 and 170.5 (C=O).

Preliminary Oxyamination Reactions.—The isoxazolidine **16** (0.5 g) was treated with hydrogen over W-2 Raney nickel at atmospheric pressure and the product was passed through a short column of silica gel to give the aziridine **17** (0.21 g, 68%). Oxidation with magnesium monoperoxyphthalate hexahydrate (0.22 g) in propan-2-ol and isolation of the product by column chromatography afforded the alkene **18** (0.16 g, 81%, identified by ^{1}H and ^{1}H–^{1}H COSY NMR spectroscopy). Oxyamination of alkene (0.14 g) was carried out in *tert*-butyl alcohol (2 cm^3) with Chloramine-T trihydrate (0.17 g) and osmium tetraoxide (solution A, 49 mm^3) as described below for the alkene **19**. Column chromatographic separation gave the adduct **25** of direct reaction (14%) and an unresolved mixture of the adducts **21** and **26** (9, 12%, respectively) which had undergone acetyl migration (identification by ^{1}H and ^{13}C NMR spectroscopy; Tables 1–3).

Silylation of the dibenzoate **19**[19] (0.13 g) was carried out with *tert*-butyldimethylsilyl chloride (TBDMSCl) (0.24 g, 1.6 mol equiv.) in pyridine (4 cm^3) for 4 h at 20 °C. Column chromatographic purification gave the silyl ether **20** (0.13 g, 73%, identified by ^{1}H and ^{1}H–^{1}H COSY NMR spectroscopy). Oxyamination of alkene **20** was carried out in *tert*-butyl alcohol (1 cm^3) with Chloramine-T trihydrate (62 mg) and osmium tetraoxide (solution A, 18 mm^3) as described for alkene **19** (below). Radial chromatography gave the unresolved oxyaminated products **22** and **27** (35 mg, 31%, 1:3.7) and the product **31** of dihydroxylation (10 mg, 12%). These were characterised by ^{1}H, ^{13}C, ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-COSY NMR spectroscopy (Tables 1–3).

Oxyamination of Alkene **19** *by using Chloroamine-T.*—The known cyclopentene **19**[19] (0.30 g) was dissolved in *tert*-butyl alcohol (4 cm^3), Chloramine-T (0.31 g, 1.2 mol equiv.) and osmium tetraoxide (solution A, 89 mm^3, 0.009 mol equiv.) were added, and the solution was kept at 45 °C for 40 h. Sodium sulfite (1 g) was added and the mixture was heated under reflux for 3 h, then was cooled. Ethyl acetate (10 cm^3) and saturated brine containing 1% sodium hydroxide (10 cm^3) were added and the mixture was shaken. The ethyl acetate phase was subsequently extracted successively with this aqueous solution

(×3) and with saturated brine, and was dried ($MgSO_4$). Removal of the solvent, and column chromatography (toluene–ethyl acetate, 2:1), gave (1S,2R,3R,4R,5S)-2,3-*dibenzoyloxy*-4-*hydroxymethyl*-5-(*tosylamino*)*cyclopentanol* **28** (0.12 g, 25%), $[\alpha]_D$ −15.2 [Found: $(M + H)^+$, 526.153 63. $C_{27}H_{28}NO_8S$ requires *m/z*, 526.153 57], and (1S,2S,3R,4R,5S)-3,4-*dibenzoyloxy*-2-*hydroxymethyl*-5-(*tosylamino*)*cyclopentanol* **23** (18 mg, 4%), m.p. 169–171 °C (from EtOH); $[\alpha]_D$ −75 (Found: C, 61.7; H, 5.5; N, 2.9. $C_{27}H_{27}NO_8S$ requires C, 61.7; H, 5.2; N, 2.7%). Unchanged starting material (0.145 g, 48%) was eluted before these products.

Oxyamination of Alkene **19** *by using Ethyl* N-*Chloro*-N-*sodiocarbamate–Silver Nitrate*.—The chlorocarbamate [26c] (0.65 g, 1.5 mol equiv.) and vacuum-dried silver nitrate (1.5 g, 3.0 mol equiv.) were stirred in acetonitrile (20 cm^3) for 5 min. A solution of alkene **19** (1.0 g) in acetonitrile (4 cm^3), osmium tetraoxide (solution B, 1.56 cm^3, 0.01 mol equiv.) and water (2.39 cm^3, 4.5 mol equiv.) were added, and the mixture was stirred for 26 h. The same amounts of chlorocarbamate and silver nitrate were then added, followed, after 5 min, by the same amounts of osmium tetraoxide solution and water. The mixture was left for a further 26 h, when further additions of half of the amounts of these materials were made. After 15 h no starting alkene remained. Aq. sodium thiosulfate (10 cm^3; 5%) was added to the filtrate and acetonitrile washings, following filtration through Celite, and the mixture was heated under reflux for 3 h. After cooling, filtration through Celite was again applied and the filtrate was reduced in volume to 10 cm^3 and extracted with dichloromethane (2 × 50 cm^3). The extract was dried ($MgSO_4$), the solvent was removed, and the residue was separated by column chromatography (toluene–ethyl acetate, 1:1 ⟶ 1:3) to give compound **29** followed by a mixture of compounds **24** and **32**, which was further resolved by radial chromatography and the following were isolated: (1S,2S,3R,4R,5R)-*ethyl* 3,4-*dibenzoyloxy*-2-*hydroxy*-5-(*hydroxymethyl*)-*cyclopentylcarbamate* **29** (0.33 g, 25%), $[\alpha]_D$ −36 [Found: $(M - H)^-$, 442.150 21. $C_{23}H_{24}NO_8$ requires *m/z*, 442.150 19]; (1S,2R,3R,4S,5S)-*ethyl* 2,3-*dibenzoyloxy*-5-*hydroxy*-4-(*hydroxymethyl*)*cyclopentylcarbamate* **24** (0.385 g, 29%), $[\alpha]_D$ −62.5 [Found: $(M - H)^-$, 442.150 23. $C_{23}H_{24}NO_8$ requires *m/z*, 442.150 19]; (1*S*,2*S*,3*R*,4*R*,5*S*)-3,4-dibenzoyloxy-5-(hydroxymethyl)cyclopentane-1,2-diol **32** (0.21 g, 19%), $[\alpha]_D$ −104.

Oxyamination of Alkene **19** *by using Ethyl* N-*Chloro*-N-*sodiocarbamate–Mercury*(II) *Trifluoroacetate*.—Mercury(II) trifluoroacetate (8.53 g, 20 mmol) was added to a stirred suspension of the chlorocarbamate salt [26c] (5.88 g, 40.5 mmol) in acetonitrile (200 cm^3), followed by addition of a solution of the alkene **19** (5.7 g, 16.9 mmol) in acetonitrile (50 cm^3), and then osmium tetraoxide (16 cm^3 solution B). The mixture was stirred for 4 days at 20 °C. Further chlorocarbamate (3.7 g), mercury(II) trifluoroacetate (5.4 g) and osmium tetraoxide solution (10 cm^3) were added and the mixture was stirred for two days. Saturated aq. sodium chloride (100 cm^3) was added and the mixture was stirred for 15 min and filtered. Sodium acetate (10 g) and aq. potassium metabisulfite (250 cm^3; 5%) were added to the filtrate, the mixture was heated under reflux for 1.5 h, and the solids and solvent were removed. The residue was partitioned between dichloromethane and water, and the organic phase was dried and concentrated. Chromatography of the residue (ethyl acetate–dichloromethane, 1:1) gave compounds **29** (1.5 g, 20%, contaminated with ethyl carbamate, 1.5 g) and **24** (2.98 g, 40%), which were identical (^1H NMR spectra) with the samples obtained above using silver nitrate.

(1S,2S,3R,4R,5R)-*Ethyl* 5-*Acetoxymethyl*-2-*acetoxy*-3,4-*dibenzoyloxycyclopentylcarbamate* **30**.—The diol **29** (30 mg) was treated in pyridine (2 cm^3) with acetic anhydride (1 cm^3) for 2 h at 20 °C. The volatiles were removed under reduced pressure, toluene (2 × 5 cm^3) was added, and evaporation was continued. Column chromatography gave the discrete *diacetate* **30** (36 mg, 100%), $[\alpha]_D$ −42 [Found: $(M + H)^+$, 528.186 49. $C_{27}H_{30}NO_{10}$ requires *m/z*, 528.186 97].

(1S,5R)-6-exo,7-endo-*Diacetoxy*-8-exo-*acetoxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octan*-3-*one* **34**.—The carbamate **24** (0.24 g) was stirred in methanol (8 cm^3) and sodium methoxide (catalytic) in methanol was added. Stirring of the mixture was continued at 20 °C for 2 h and was followed by heating under reflux for 2.5 h. The solution was cooled, the sodium ions were removed using Dowex (H^+) resin, and the methanol was evaporated off to give syrupy triol **33**, which was treated with pyridine (2 cm^3) and acetic anhydride (1 cm^3) for 24 h at 20 °C. Dichloromethane (25 cm^3) was added and the solution was extracted with hydrochloric acid (1 mol dm^{-3}), washed with water, and dried ($MgSO_4$). Removal of the solvent and filtration through silica gel (ethyl acetate as solvent) gave the acetylated cyclic carbamate **34** (0.14 g, 86%), $[\alpha]_D$ −25 (lit.,[11,12] $[\alpha]_D$ −25, −24.1). ^1H and ^{13}C NMR spectra were consistent with literature data.[11,12]

Tri-O-*acetylallosamizoline* **37**.—To a solution of the oxazolidinone **34** (0.20 g, 0.63 mmol) in dry dichloromethane (1 cm^3) were added powdered 4 Å molecular sieve (0.2 g) and trimethyloxonium tetrafluoroboranuide (0.28 g, 1.89 mmol). The mixture was stirred at 20 °C under argon for 24 h. A solution of dimethylamine (0.27 g, 6 mmol) in dichloromethane (1.5 cm^3), previously stirred with powdered molecular sieve for 30 min, was added and the mixture was stirred for another 24 h. The reaction mixture was diluted with dichloromethane (10 cm^3) and poured into saturated aq. sodium hydrogen carbonate. The phases were separated and the aqueous layer was reextracted with dichloromethane (2 × 15 cm^3). The organic phase was washed with water, dried ($MgSO_4$), and the solvent was removed, and flash chromatography of the residue (ethyl acetate ⟶ ethyl acetate–methanol, 10:1) gave the title compound (0.175 g, 81%), $[\alpha]_D$ +65.1 (lit.,[12] $[\alpha]_D$ +28.8). ^1H and ^{13}C NMR spectra were consistent with literature data.[3,12]

Allosamizoline **2**.—A solution of the triacetate **37** (0.08 g) in methanol (2 cm^3) containing sodium methoxide (0.1 mol dm^{-3} in methanol; 0.05 cm^3) was stirred at 20 °C for 5 h. Removal of the solvent and flash chromatography (methanol–triethylamine, 200:1) of the residue gave crystalline allosamizoline **2** (0.049 g, 97%), m.p. 82–85 °C; $[\alpha]_D$ +4.2 (*c* 3, water). For comparison with literature data, a small sample was converted into the hydrochloride by dissolution in methanolic hydrogen chloride (1 mol dm^{-3}; 0.2 cm^3), followed by removal of the volatiles; $[\alpha]_D$ −21.0 (lit.,[2] $[\alpha]_D$ −22.2; lit.,[12] −21.7) [Found: $(M + H)^+$, 217.1197. $C_9H_{17}N_2O_4$ requires *m/z*, 217.1188]. ^1H and ^{13}C NMR data were consistent with literature data.[2,3,12]

(1S,5R)-6-exo,7-endo-*Dibenzoyloxy*-8-exo-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octan*-3-*one* **35**.—A solution of the ethyl carbamate **24** (2.70 g) and bis(tributyltin) oxide (5.0 cm^3) in toluene (80 cm^3) was heated under reflux with removal of ethanol for 10 h. The solvent was removed, and chromatography of the residue (ethyl acetate–dichloromethane, 1:1) afforded the *cyclic carbamate* **35** (1.75 g, 72%), $[\alpha]_D$ −63.5 [Found: $(M + H)^+$, 398.1232. $C_{21}H_{20}NO_7$ requires *m/z*, 398.1240].

(1S,5R)-6-exo,7-endo-*Dibenzoyloxy*-8-exo-*benzyloxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octan*-3-*one* **36**.—TFSA (4 drops) was

added to a stirred solution of the alcohol **35** (0.35 g) and benzyl trichloroacetimidate (0.65 cm^3, 4 mol equiv.) in dry dichloromethane–cyclohexane (40 cm^3; 1:1 v/v).[28] After 3 h the same amounts of reagents were added again and the mixture was stirred for another 15 h. More TFSA (4 drops) was added, and after another 4 h the solution was washed with aq. sodium hydrogen carbonate. The organic phase was dried and concentrated, and chromatography of the residue (ethyl acetate–light petroleum, 1:2) gave *benzyl ether* **36** (0.30 g, 70%), $[\alpha]_D$ −21.5 [Found: $(M + H)^+$, 488.1711. $C_{28}H_{26}NO_7$ requires *m/z*, 488.1709].

(1S,5S)-6-exo,7-endo-*Dibenzoyloxy*-8-exo-*benzyloxymethyl*-3-*dimethylamino*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*ene* **38**.—The oxazolidinone **36** (2.0 g, 4.1 mmol) was treated consecutively with trimethyloxonium tetrafluoroboranuide (2.40 g, 16.2 mmol) and dimethylamine (1.84 g, 40.8 mmol) as described above for the preparation of allosamizoline triacetate **37** from compound **34**. After purification by flash chromatography (ethyl acetate) the *title compound* **38** (1.61 g, 76%) was obtained as a foam, $[\alpha]_D$ +6.6 [Found: $(M + H)^+$, 515.2171. $C_{30}H_{31}N_2O_6$ requires *m/z*, 515.2182].

(1S,5R)-8-exo-*Benzyloxymethyl*-3-*dimethylamino*-6-exo,7-endo-*dihydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*ene* **39**.—A solution of the dibenzoate **38** (2.0 g, 3.89 mmol) in methanol (40 cm^3) containing sodium methoxide (0.2 mol dm^{-3} in methanol; 1.0 cm^3) was stirred for 16 h at 20 °C. Removal of the solvent, and purification of the residue by flash chromatography (methanol–triethylamine, 200:1), gave the *title compound* **39** (1.12 g, 94%). Crystallised from ethyl acetate–light petroleum it had m.p. 148–149 °C, $[\alpha]_D$ +14.9 (lit.,[9] m.p. 139–143 °C) [Found: $(M + H)^+$, 307.1651. $C_{16}H_{23}N_2O_4$ requires *m/z*, 307.1658].

Allyl 2-*Acetamido*-4,6-O-*benzylidene*-2-*deoxy*-3-O-*methanesulfonyl*-β-D-*glucopyranoside* **41**.—Methanesulfonyl chloride (2.5 cm^3) was added to a stirred solution of the known free alcohol **40**[30] (5 g) in pyridine (25 cm^3) at 0 °C. After 16 h at 4 °C the reaction mixture was poured into ice–water to give a crystalline product (5.4 g, 89%). Recrystallisation from methanol gave the *title compound* **41**, m.p. 202–203 °C; $[\alpha]_D$ −41.6 (Found: C, 53.4; H, 5.7; N, 3.2; S, 7.5. $C_{19}H_{25}NO_8S$ requires C, 53.4; H, 5.9; N, 3.3; S, 7.5%).

Allyl 2-*Acetamido*-4,6-O-*benzylidene*-2-*deoxy*-β-D-*allopyranoside* **44**.—The mesyl ester **41** (1.66 g) was heated with sodium acetate (1.66 g) in 2-methoxyethanol–water (17 cm^3; 95:5) in a sealed tube for 9 h at 125 °C. The reaction mixture was cooled, and poured into water to give a crystalline product (1.2 g, 91%). Recrystallisation from ethanol gave the title compound **44**, m.p. 256–259 °C; $[\alpha]_D$ −92.6 (lit.,[13b] m.p. 251–252 °C; $[\alpha]_D$ −90.4).

Allyl 2-*Acetamido*-3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-β-D-*allopyranoside* **45**.—The alcohol **44** (7.0 g) was stirred in dry DMF (200 cm^3) containing benzyl bromide (6 cm^3) with barium oxide (13 g) and barium hydroxide octahydrate (4 g) at 20 °C for 16 h. Chloroform (200 cm^3) was added followed by aq. acetic acid (55 cm^3; 10%), with cooling of the mixture. The chloroform layer was washed successively with aq. sodium hydrogen carbonate and water, and dried ($MgSO_4$). Removal of the solvent gave a crystalline residue (8.3 g, 94%). Recrystallisation from methanol afforded the *title compound* **45**, m.p. 217–219.5 °C; $[\alpha]_D$ −118.5 (Found: C, 68.1; H, 6.7; N, 3.1. $C_{25}H_{29}NO_6$ requires C, 68.3; H, 6.6; N, 3.2%).

Prop-1-*enyl* 3-O-*Benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **46**.—(i) *By base treatment of the* N-*acetyl derivative* **45**. Compound **45** (0.40 g) was heated in methanolic potassium hydroxide (8 cm^3; 32% w/w) in a sealed tube at 125 °C for 48 h. After the mixture had been cooled, most of the solvent was removed and the residue was partitioned between chloroform (40 cm^3) and water (10 cm^3). The chloroform phase was dried ($MgSO_4$), reduced in volume to 10 cm^3, and treated at 20 °C with phthalic anhydride (0.13 g) for 20 min. The solvent was removed and the residue was heated in pyridine–acetic anhydride (3 cm^3; 2:1) for 5 h at 125 °C. Removal of the solvents gave a brown residue, which was resolved by flash chromatography (toluene–ethyl acetate, 10:1) to give the *title compound* **46** (0.34 g, 71%), $[\alpha]_D$ −138.0 (Found: C, 70.4; H, 5.7; N, 2.6. $C_{31}H_{29}NO_7$ requires C, 70.6; H, 5.5; N, 2.7%).

(ii) *By allyl rearrangement of the glycoside* **49**. [Ir(cycloocta-1,5-diene)$(PMePh_2)_2$]PF_6 (17 mg, 0.020 mmol) was added under argon to a stirred solution of allyl glycoside **49** (see below) (0.100 g, 0.23 mmol) in dry tetrahydrofuran (THF) (10 cm^3). The orange solution was degassed, left under hydrogen until yellow, briefly degassed again, and left under argon for 1.5 h. Evaporation of the solvent gave a foam, which was purified by flash chromatography (toluene–ethyl acetate, 10:1) to afford the propenyl glycoside **46** (89 mg, 89%). The product was identical (^1H NMR spectrum) with that produced from the *N*-acetyl derivative **45**.

3-O-*Benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranose* **47**.—Compound **46** (0.50 g) was dissolved in acetone–water (18 cm^3; 5:1) containing mercury(II) chloride (0.50 g) and the solution was kept at 20 °C for 3 h. The acetone was removed by evaporation and the residue was partitioned between ethyl acetate and aq. ammonium chloride (sat.). After being washed with water and dried ($MgSO_4$) the solvent was removed from the organic phase to leave a syrup, which was purified by crystallisation from toluene–light petroleum to give the free sugar **47** (0.42 g, 91%), m.p. 156–157 °C; $[\alpha]_D$ −145.5 (lit.,[13b] m.p. 149–150.3 °C; $[\alpha]_D$ −114.1).

Allyl 3-O-*Benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **49**.—(i) *From the* N-*acetyl derivative* **45**. Compound **45** (0.40 g), methanolic potassium hydroxide (4 cm^3; 32% w/w), methanol (3.2 cm^3) and water (0.8 cm^3) were heated in a sealed tube at 125 °C for 5 days. The reaction mixture was phthaloylated as for the hydrolysate of compound **45** and the product was purified by flash chromatography (toluene–ethyl acetate, 10:1) to give the *title compound* **49** (0.32 g, 61%), $[\alpha]_D$ −132.4 (Found: C, 70.4; H, 5.6; N, 2.6. $C_{31}H_{29}NO_7$ requires C, 70.6; H, 5.5; N, 2.7%).

(ii) *From the alcohol* **50**. To a solution of alcohol **50** (see below) (65 mg, 0.15 mmol) in DMF (5 cm^3) was added sodium hydride (8 mg, 0.33 mmol), followed by benzyl bromide (0.05 cm^3, 0.47 mmol). After being stirred at ambient temperature for 24 h, the reaction mixture was diluted with ethyl acetate and washed successively with 10% hydrochloric acid, water, saturated aq. sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (light petroleum–ethyl acetate, 3:1) gave the benzyl ether **49** (64 mg, 82%), identical ($[\alpha]_D$, NMR spectra) with the sample obtained from compound **45**.

Allyl 4,6-O-*Benzylidene*-2-*deoxy*-2-*phthalimido*-3-O-*trifluoromethanesulfonyl*-β-D-*glucopyranoside* **43**.—To a stirred solution of allyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside **42**[30] (0.50 g, 1.14 mmol) and pyridine (0.30 cm^3, 3.6 mmol) in dichloromethane (10 cm^3) at −30 °C under argon was added dropwise trifluoromethanesulfonic anhydride (0.32 cm^3, 1.8 mmol). After being warmed to ambient temperature over a period of 30 min, the solution was diluted with dichloromethane, washed successively with 10% hydrochloric

acid, water, saturated aq. sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (light petroleum–ethyl acetate, 5:1) gave the *triflate* **43** (0.55 g, 84%) as a foam, $[\alpha]_D$ −32.6 [Found: $(M + NH_4)^+$, 587.1330. $C_{25}H_{26}F_3N_2O_9S$ requires *m/z*, 587.1331].

Allyl 4,6-O-*Benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **50**.—A solution of triflate **43** (0.110 g, 0.19 mmol) and tetrabutylammonium nitrite (0.146 g, 0.52 mmol) in DMF (5 cm^3)[32] was stirred at 55 °C for 3 h. After being cooled to ambient temperature the solvent was removed under reduced pressure to give a syrup, which on purification by flash chromatography (light petroleum–ethyl acetate, 3:1) furnished the crystalline *title compound* **50** (52 mg, 62%). Recrystallised from light petroleum–toluene it had m.p. 103–106 °C; $[\alpha]_D$ −66.4 [Found: $(M - CH_2{=}CHCH_2O)^+$, 380.1134. $C_{21}H_{18}NO_6$ requires *m/z*, 380.1134].

Allyl 3,6-*Di*-O-*benzyl*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **51**.—To a stirred, cooled solution of compound **49** (0.5 g) in THF (10 cm^3) containing sodium cyanoboranuide (0.60 g) and powdered 4 Å molecular sieve (0.10 g), was added dropwise a solution of hydrogen chloride in diethyl ether (1 mol dm^{-3}; 8.0 cm^3). After 30 min at 0 °C the reaction mixture was filtered through Celite, the filtrate was partitioned between dichloromethane (40 cm^3) and aq. sodium hydrogen carbonate (10 cm^3), and the dichloromethane layer was washed with water and dried ($MgSO_4$). Removal of the solvent, and purification of the residue by flash chromatography, gave the *title compound* **51** (0.39 g, 78%), $[\alpha]_D$ −92.2 [Found: $(M + H)^+$, 530.2193. $C_{31}H_{32}NO_7$ requires *m/z*, 530.2179].

Allyl 3,6-*Di*-O-*benzyl*-4-O-(3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranosyl*)-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **52**.—To a stirred solution of compound **47** (0.75 g) and trichloroacetonitrile (2.0 cm^3) in dry dichloromethane (5 cm^3) containing powdered 4 Å molecular sieve (0.5 g) was added a solution of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (0.03 cm^3) in the same solvent (0.3 cm^3) at 0 °C under argon. After 15 min the reaction mixture was passed through a short column of silica gel (light petroleum–ethyl acetate, 2:1). Concentration of the eluate gave a crystalline residue of trichloroacetimidate **48**, which was dissolved in dry dichloromethane (5 cm^3). This solution was added to a stirred solution of compound **51** (0.72 g) in dry dichloromethane (15 cm^3), containing powdered 4 Å molecular sieve (0.5 g), at − 30 °C, followed after 10 min by a solution of trimethylsilyl triflate (0.004 cm^3) in the same solvent (0.08 cm^3). After 15 min the reaction mixture was filtered through Celite, and the filtrate was diluted with dichloromethane, washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography to give the *title disaccharide derivative* **52** (1.16 g, 85%), $[\alpha]_D$ −119.9 [Found: $(M + H)^+$, 999.3743. $C_{59}H_{55}N_2O_{13}$ requires *m/z*, 999.3704].

3,6-*Di*-O-*benzyl*-4-O-(3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranosyl*)-2-*deoxy*-2-*phthalimido*-β-D-*allopyranose* **53**.—To a solution of compound **52** (0.70 g) and 1,4-diazabicyclo[2.2.2]octane (0.10 g) in refluxing ethanol–benzene–water (7:3:1) (33 cm^3) was added tris(triphenylphosphine)rhodium(I) chloride (0.10 g). After being heated under reflux for 24 h, the cooled solution was diluted with ethyl acetate (30 cm^3), washed with brine, and dried ($MgSO_4$). The residue obtained on removal of the solvent was treated with mercury(II) chloride (0.35 g) in acetone–water (30 cm^3; 5:1) as described for the preparation of compound **47** to give the crystalline free sugar **53** (0.49 g, 73%), m.p. 129–132 °C; $[\alpha]_D$ −127.1 (lit.,[13b] $[\alpha]_D$ −127.8).

(1S,5R)-8-exo-*Benzyloxymethyl*-3-*dimethylamino*-6-exo-*hydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*en*-7-endo-*yl* 3,6-*Di*-O-*benzyl*-4-O-(3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranosyl*)-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **55** *and* (1S,5S)-8-exo-*Benzyloxymethyl*-3-*dimethylamino*-7-endo-*hydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*en*-6-exo-*yl* 3,6-*Di*-O-*benzyl*-4-O-(3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-2-*phthalimido*-β-D-*allopyranosyl*)-2-*deoxy*-2-*phthalimido*-β-D-*allopyranoside* **56**.—To a solution of compound **53** (1.15 g, 1.21 mmol) and trichloroacetonitrile (2.0 cm^3) in dry dichloromethane (15 cm^3) stirred at 0 °C under argon was added powdered 4 Å molecular sieve (1.0 g), followed by a solution of DBU (0.04 cm^3) in dichloromethane (0.3 cm^3). After 15 min, the reaction mixture was passed through a short column of silica gel (light petroleum–ethyl acetate, 2:1). Concentration of the eluate gave a crystalline residue **54** (1.12 g, 84%), which was dissolved in dry dichloromethane (20 cm^3). This solution was added to a stirred solution of allosamizoline derivative **39** (0.37 g, 1.20 mmol) in dry dichloromethane (10 cm^3) containing 4 Å molecular sieve (0.4 g) at 0 °C, followed after 5 min by trimethylsilyl triflate (0.220 cm^3, 1.13 mmol). After 30 min at 0 °C and 10 min at 20 °C the reaction mixture was filtered through Celite, diluted with dichloromethane, washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (dichloromethane–methanol, 20:1 ⟶ 10:1) to give a ~5:1 mixture of the title compounds (0.85 g, 68%).

(1S,5R)-8-exo-*Benzyloxymethyl*-3-*dimethylamino*-6-exo-*hydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*en*-7-endo-*yl* 2-*Acetamido*-4-O-(2-*acetamido*-3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-β-D-*allopyranosyl*)-3,6-*di*-O-*benzyl*-2-*deoxy*-β-D-*allopyranoside* **57** *and* (1S,5S)-8-exo-*Benzyloxymethyl*-3-*dimethylamino*-7-endo-*hydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*en*-6-endo-*yl* 2-*Acetamido*-4-O-(2-*acetamido*-3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-β-D-*allopyranosyl*)-3,6-*di*-O-*benzyl*-2-*deoxy*-β-D-*allopyranoside* **58**.—A solution of the mixed isomers **55** and **56** (0.57 g, 0.45 mmol) in ethanol (14 cm^3)–aq. methylamine (40%; 8.5 cm^3) was kept at ambient temperature for 48 h. The ethanol was removed under reduced pressure, and the water by freeze drying. The *N,N'*-dimethylphthalic diamide generated in the reaction was removed by flash chromatography (ethyl acetate–methanol, 10:1). The mixed diamines (0.35 g, 79%) were dissolved in methanol (20 cm^3), acetic anhydride (1 cm^3) was added with stirring of the mixture at − 10 °C, and the solution was kept at this temperature for 16 h. After hydrolysis of the unchanged acetic anhydride by slow addition of triethylamine (1.1 cm^3), partitioning between dichloromethane and water and concentration of the organic phase gave a syrup, which was fractionated by flash chromatography (ethyl acetate–methanol, 10:1 ⟶ 5:2) to give *minor isomer* **58** (68 mg, 18%). Recrystallised from methanol it had m.p. 175–177 °C, $[\alpha]_D$ −37.8 [Found: $(M + H)^+$, 1071.4977. $C_{60}H_{71}N_4O_{14}$ requires *m/z*, 1071.4967]; δ_H(500 MHz) (*inter alia*) 2.1 (1 H, m, 8^c-H), 3.6 (4 H, m, 6^b-H_2, 8^c-H and 6^c-H), 3.67 (1 H, dd, $J_{4,5}$ 9.7, 4^b-H), 3.7 (2 H, m, 4^a- and $8'^c$-H), 3.75 (1 H, t, 6^a-H), 3.79 (1 H, dd, $J_{6,7}$, $J_{7,8}$ 7.8 or 10.4, 7^c-H), 3.92 (1 H, dt, $J_{2,3}$ 2.5, 2^b-H), 4.1 (5 H, m, 2^a-, 3^a-, 5^a-, 5^b- and 5^c-H), 4.25 (1 H, t, $J_{3,4}$ 2.5, 3^b-H), 4.47 (1 H, dd, $J_{5,6}$ 5.1, $J_{6,6'}$ 10.5, 6^a-H), 4.67 (1 H, d, $J_{1,2}$ 8.3, 1^a-H), 4.72 (1 H, dd, $J_{1,8}$ 9.0, $J_{1,8}$ 6.8, 1^c-H), 4.76 (1 H, d, $J_{1,2}$ 8.5, 1^b-H), 5.69 (1 H, d, J_{NH} 8.8, NH) and 6.5 (1 H, d, J_{NH} 8.8, NH); δ_C 50.3 (C-8^c), 52.4 (C-2^a), 52.7 (C-2^b), 63.7 (C-5^c), 68.0 (C-$8'^c$), 69.1 (C-6^a), 69.4 (C-6^b), 71.4 (C-5^a), 72.0 (C-5^b, -7^c), 75.4 (C-3^a), 77.0 (C-3^b), 78.6 (C-4^b), 80.0 (C-4^a), 81.3 (C-1^c), 95.7 (C-6^c), 100.4 (C-1^b) and 102.1 (C-1^a).

This was followed by the major isomer **57** (300 mg, 79%), $[\alpha]_D$ −36.5 (lit.,[13b] −35). ^1H and ^{13}C NMR spectra were consistent with literature data.[13b]

Allosamidin **1**.—Compound **57** (45 mg) was hydrogenated over palladium on charcoal (10%; 30 mg) at 55 psi for 48 h. After addition of more catalyst (30 mg) the hydrogenation was continued for another 48 h. Removal of the solids by filtration through glass-fibre and of the solvent by evaporation gave allosamidin **1** as a fine powder (24.3 mg, 93%), $[\alpha]_D$ −25.5 (lit.,[2,6,13] −24.8, −21.7, −21.4); ^1H and ^{13}C NMR spectra were consistent with literature data.[2,13]

(1S,5S)-3-*Dimethylamino*-8-exo-*hydroxymethyl*-7-endo-*hydroxy*-2-*oxa*-4-*azabicyclo*[3.3.0]*oct*-3-*en*-6-exo-*yl* [2-*Acetamido*-4-O-(2-*acetamido*-2-*deoxy*-β-D-*allopyranosyl*)-2-*deoxy*-β-D-*allopyranoside* **59**.—Compound **58** (30 mg) was hydrogenolysed as described for compound **57**. The *title compound* **59** was obtained as a fine powder (16.0 mg, 92%), $[\alpha]_D$ −31.5 (water) [Found: $(M + H)^+$, 623.2746. $C_{25}H_{43}N_4O_{14}$ requires *m/z*, 623.2776]; δ_H(500 MHz; D_2O; acetone as reference) 2.53 (1 H, ddd, $J_{1.8}$ 4.5, $J_{8.7}$ 7, 8^c-H), 3.7 (4 H, m, 6^a- and 6^b-H_2), 3.72 (1 H, dd, 8′^{c}-H), 3.76 (1 H, dd, $J_{3.4}$, 2.5, 4^a-H), 3.85 (1 H, dd, $J_{3.4}$ 2.5, 4^b-H), 3.88 (1 H, dd, 8′^{c}-H), 3.9 (2 H, m, 5^a- and 5^b-H), 3.96 (1 H, dd, $J_{1.2}$ 8.6, $J_{2.3}$ 2.5, 2^a-H), 4.00 (1 H, dd, $J_{1.2}$ 8.6, $J_{2.3}$ 2.5, 2^b-H), 4.05 (1 H, dd, $J_{7.6}$ 6, 7^c-H), 4.12 (1 H, dd, 3^b-H), 4.30 (1 H, dd, $J_{5.6}$ 4, 6^c-H), 4.46 (1 H, dd, 3^b-H), 4.48 (1 H, dd, $J_{1.5}$ 8.7, 5^c-H), 4.87 (1 H, d, 1^b-H), 4.97 (1 H, d, 1^a-H) and 5.43 (1 H, ddd, 1^c-H); δ_C 52.5 (C-8^c), 52.7 (C-2^b), 53.6 (C-2^a), 59.8 (C-8′^{c}), 61.4 (C-6^a), 61.7 (C-6^b), 63.9 (C-5^c), 67.1 (C-4^a), 69.9 (C-3^b), 70.9 (C-3^a), 73.4 (C-5^b), 74.2 (C-5^a), 74.8 (C-7^c), 77.2 (C-4^b), 87.9 (C-1^c), 88.2 (C-6^c), 98.6 (C-1^a) and 101.3 (C-1^b).

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