Total Synthesis of the Trehalase Inhibitors Trehalostatin and Trehazolin, and of Their Diastereoisomers. Final Structural Confirmation of the Inhibitor

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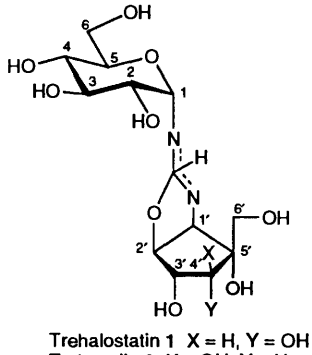
Potent trehalase inhibitors **1**–**4** have been synthesized, thereby establishing both the structure and the absolute configuration of the known inhibitor trehazolin **2**. Compound **1**, previously proposed as the structure of trehalostatin, and its diastereoisomer **3**, have been shown not to possess any observable inhibitor activity against trehalase. These results indicate that the initial structure assigned for trehalostatin is incorrect, and that its structure is identical with that of trehazolin **2**.

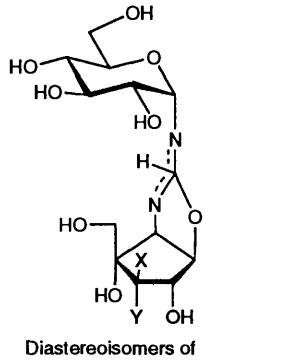
In 1990, trehalostatin, a potent and specific inhibitor against blowfly (*Aldrichna grahami*) trehalase, was isolated by Murao *et al.*[1,2] from the culture broth of *Amycolatopsis trehalostatica* and the structure[3] initially proposed was revised as depicted† in structure **1** mainly on the basis of ^{1}H NMR spectroscopic data. On the other hand, Ando *et al.*[4] later reported the isolation of the strong trehalase inhibitor trehazolin **2** from the culture broth of *Micromonospora* strain SANK 62390, and suggested it to be identical with trehalostatin by comparison of biochemical and spectroscopic data. They, however, assigned a different structure, the 4′-epimer **2**, to it.

Recently, synthesis[5] of the aminocyclitol moiety of trehazolin **2**, followed by a complete synthesis[6,7] of the whole molecule of the inhibitor and its diastereoisomer **4**, clearly established the structure proposed for compound **2**, combined with its absolute configuration. Therefore, the question still remained unanswered as to whether or not trehalostatin and trehazolin are identical or if the former is in fact the 4′-epimer of compound **2**. Very recently, we finally obtained an answer[8] to this puzzle by a total synthesis of compound **1** and its diastereoisomer **3**, and by a demonstration of their complete lack of inhibitory activity against trehalase: the trehalostatin structure previously assigned as **1** is incorrect and the two inhibitors are identical, with structure **2**.

In this paper, we describe in detail our studies on a total synthesis of compounds **1** and **2**, our establishment of the absolute configuration of compound **2**, and biological assay of the inhibitors and their analogues, together with some considerations on the structure–inhibitory activity relationship of inhibitors of this kind.

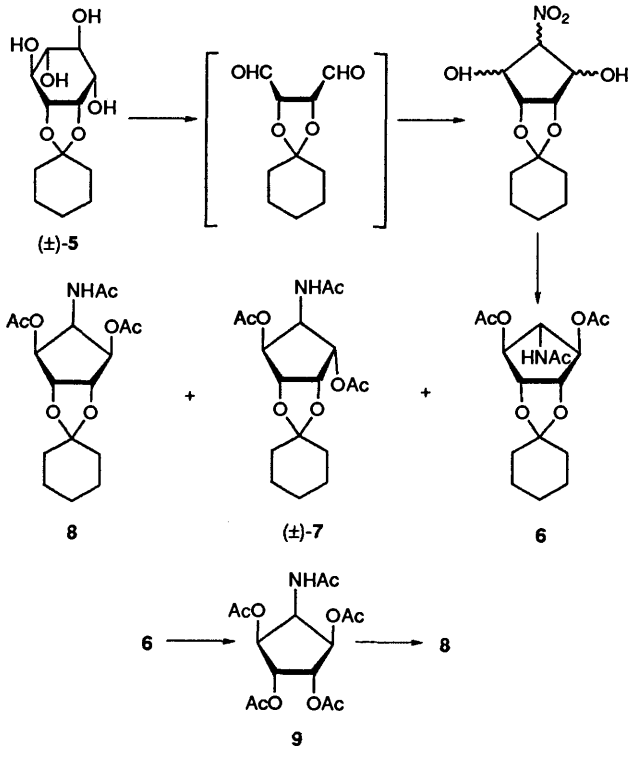


Trehalostatin **1** X = H, Y = OH
Trehazolin **2** X = OH, Y = H



Diastereoisomers of
Trehalostatin **3** X = H, Y = OH
Trehazolin **4** X = OH, Y = H

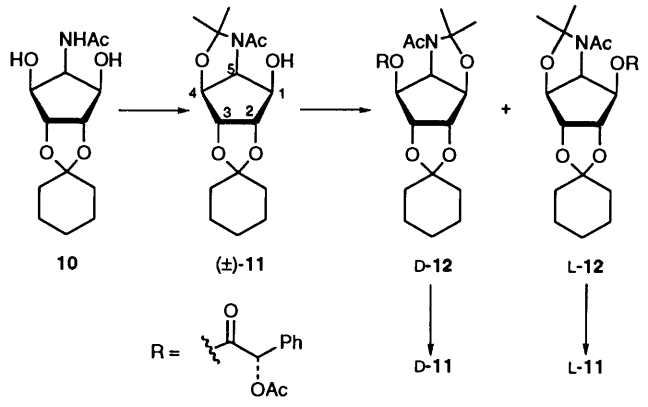
† For convenience, the structure of compound **1** depicts one of the diastereoisomers, the absolute configuration of which is related to that of trehazolin **2**.



Scheme 1 For convenience, the structures of the racemic compounds (±)-**5** and (±)-**7** depict only one of the respective enantiomers

Synthesis of Optically Active 5-Amino-1-C-hydroxymethyl-cyclopentane-1,2,3,4-tetraols.‡—Base-catalysed nitromethane condensation[10] of the dialdehyde generated by periodate oxidation of (±)-1,2-*O*-cyclohexylidene-*myo*-inositol[11] (±)-**5** gave a mixture of the nitro-diols, which was hydrogenated in the presence of Raney nickel, followed by acetylation with acetic anhydride in pyridine, to afford three diastereoisomeric 2,3-*O*-cyclohexylidene derivatives **6** (~40%), (±)-**7** (~5%), and **8** (~5%) of 5-acetamido-1,4-*O*-acetylcyclopentane-1,2,3,4-tetraol. Since we needed the minor product **8** for the present syntheses, an attempt was made to convert the readily accessible epimer **6** into compound **8**, *via* the penta-*N*,*O*-acetyl derivative

‡ In this paper, nomenclature of cyclitols follows IUPAC–IUB 1973 Recommendations for Cyclitols (ref. 9). The stereochemical features of cyclitols are shown by a fractional notation whereby numerals in the numerator denote hydroxy or other groups above the plane of the ring while numerals in the denominator denote hydroxy or other groups below that plane.



Scheme 2 For convenience, the structure of the racemic compound (±)-**11** depicts only one of the respective enantiomers

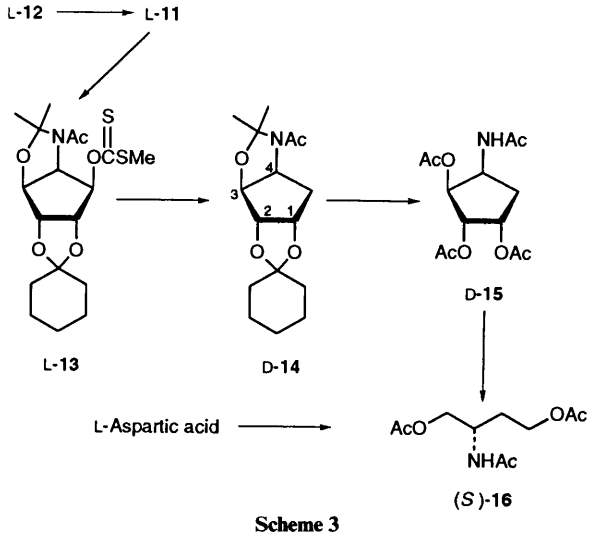
9, following the reported 5-step reaction[12] and successive *O*-cyclohexylidenation and acetylation.

The diol **10** obtained by Zemplén de-*O*-acetylation of compound **8** was converted into the *N*,*O*-isopropylidene derivative (±)-**11**,[5] which was transformed into a diastereoisomeric mixture of the (*S*)-acetylmandelates D- and L-**12** by treatment with the corresponding acid in the presence of dicyclohexylcarbodiimide (DCC) in CH_2Cl_2. The mixture was easily separated by column chromatography on silica gel to give D-(42%) and L-**12*** (39%), de-*O*-acylation of which afforded cyclopentanols D- and L-**11**, respectively, in nearly quantitative yield.

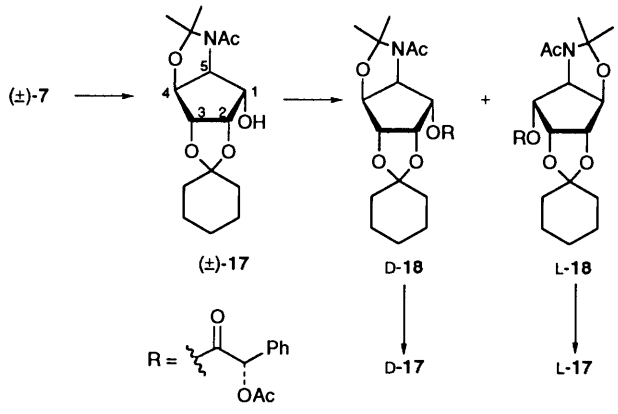
Alternatively, the minor compound (±)-**7** was de-*O*-acetylated, *N*,*O*-isopropylidenated [→ (±)-**17**], and then similarly optically resolved by chromatographic separation of the (*S*)-acetylmandelates (→ D- and L-**18**). The absolute configurations of each enantiomeric alcohol D- and L-**17** regenerated by de-*O*-acylation of the esters **18** were later correlated to those of their epimers L- and D-**11**, respectively.

Absolute configurations of alcohols D- and L-**11** were established by transforming them into optically active (*R*)- and (*S*)-2-acetamidobutane-1,4-diol diacetate, respectively, the latter of which was identified with an authentic sample derived from L-aspartic acid. Thus, deoxygenation of compound L-**11** was effected by converting it into the methylthiothiocarbonyl derivative L-**13**, followed by treatment with tributyltin hydride in the presence of azoisobutyronitrile (AIBN), to give the 1,2-*O*-cyclohexylidene-3,4-*N*,*O*-isopropylidene derivative D-**14** of 1D-(1,2/3,4)-4-acetamidocyclopentane-1,2,3-triol. The protecting groups were removed by acid hydrolysis, and the product was isolated and characterised as the tetra-*N*,*O*-acetyl derivative D-**15**. This compound was de-O-acetylated and then treated with excess of sodium periodate followed by reduction with sodium borohydride. The diol thus obtained was acetylated to give (*S*)-2-acetamidobutane-1,4-diol diacetate (*S*)-**16**, $[\alpha]_D$ −43 ($CHCl_3$), which was identical in all respect with an authentic sample, $[\alpha]_D$ −42 ($CHCl_3$), obtained by conventional acetylation of the amino alcohol derived[13] from L-aspartic acid diethyl ester. These results unambiguously supported the 1*R*-configuration of L-**11**. Likewise, the enantiomeric (*R*)-**16**, $[\alpha]_D$ +42 ($CHCl_3$), was obtained from D-**11**.

Optically active 5-aminocyclopentane-1,2,3,4-tetraols thus prepared were converted into the branched-chain aminocyclitol moieties of the inhibitors **1** and **2** according to the procedures previously employed[5] for the preparation of the racemic compounds. Thus, oxidation of compound L-**11** gave the ketone D-**19**, which was transformed into the exo-olefin compound D-**20** (45% overall yield) *via* the spiro epoxide, the enone D-**21** (11%) being obtained as a side product. Treatment of D-**20** with osmium tetraoxide in aq. acetone followed by conventional decyclohexylidenation, deisopropylidenation, and acetylation gave two branched aminocyclitols D-**22** (49%) and L-**23** (51%), which afforded the respective free amino alcohols D-**24** and L-**25** almost quantitatively by acid hydrolysis followed by purification over Dowex 50W-X2 (H^+) resin with aq. ammonia as the eluent. The antipodes L-**24** and D-**25** were prepared from alcohol D-**11** following a similar sequence of reactions (→L-**19**→L-**20**→L-**22** and D-**23**).



Scheme 3

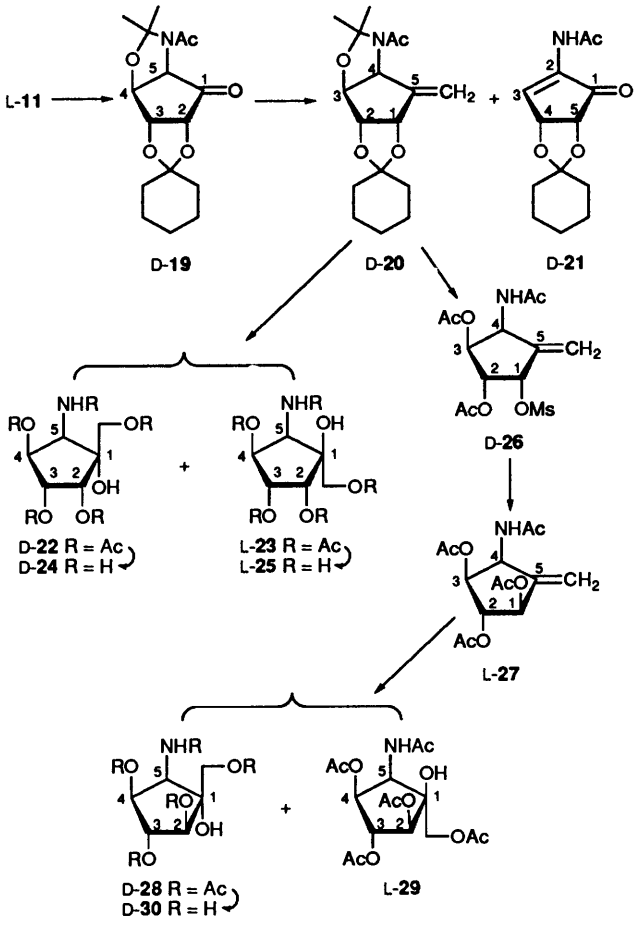


Scheme 4 For convenience, the structure of the racemic compound (±)-**17** depicts only one of the respective enantiomers

The absolute configurations of the alcohols D- and L-**17** were established by converting them into the ketones D- and L-**19**, respectively.

On the other hand, compound D-**20** was deprotected and the triol obtained was selectively mesylated at the allylic position, to give, after acetylation, the mesyl ester D-**26** (68%). Treatment of compound D-**26** with sodium acetate in aq. *N*,*N*-dimethylformamide (DMF) resulted in inversion of the configuration of C-1 to give the tetra-*N*,*O*-acetyl derivative L-**27** (66%). Oxidation of compound L-**27** with osmium tetraoxide in aq.

* Following the rule, the absolute configuration of a cyclitol is specified by making a vertical Fischer–Tollens type of projection of the structure, with C-1 at the top and with C-2 and C-3 on the front edge of the ring. The configuration is then designated as D if the hydroxy group at the lowest-numbered chiral centre projects to the right, and as L if it projects to the left.



Scheme 5

acetone followed by acetylation afforded two compounds, D-**28** (87%) and L-**29** (13%). Acid hydrolysis of compound **28** provided the free base D-**30** quantitatively. Likewise, the antipode L-**30** was prepared from compound L-**20**.

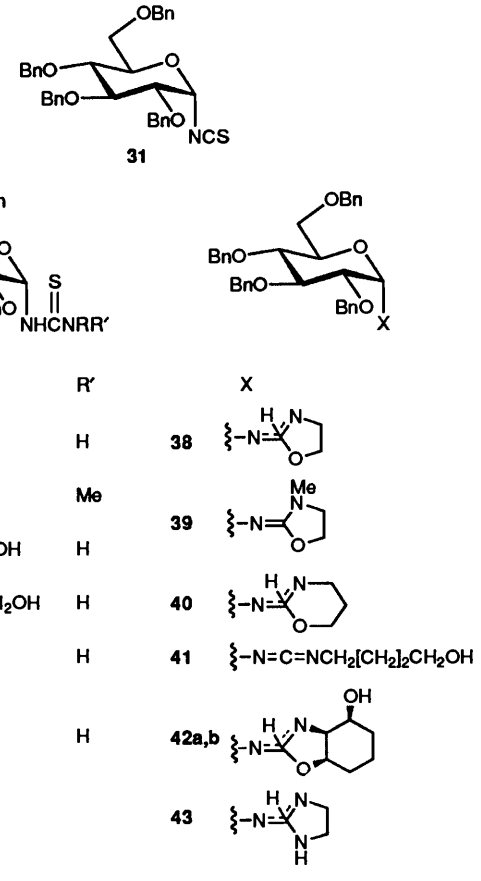
Synthesis of Several α-Glucosylaminodihydrooxazoles. Simple formation of isoureides from thiourea derivatives.—The α-glycosylaminodihydrooxazole structures as seen in trehalostatin and trehazolin **2** are very rare examples in natural product chemistry. Few synthetic studies have therefore been carried out systematically to prepare such compounds so far. Recently, Mota and co-workers[14] reported a synthesis of some 2-glycosylamino-4,5-dihydrooxazole derivatives from the corresponding β-glycosyl β-iodourea derivatives by heating them in anhydrous DMF through an intramolecular S_N2 displacement reaction.

Since it seemed rather difficult to introduce a leaving group into the appropriate substrates for preparation of the whole structures of the inhibitors, attempts were first made to construct an isoureido ring by cyclisation of a carbodiimide derivative through participation of a neighbouring hydroxy function. Thus, several α-glucopyranosyl thiourea derivatives **32**–**36** were prepared by coupling of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl isothiocyanate[15] **31** with the corresponding amino alcohols: 2-aminoethanol, 2-(methylamino)ethanol, 3-aminopropan-1-ol, 4-aminobutan-1-ol, and (1,2,3/0)-2-aminocyclohexane-1,3-diol,[16] respectively, in the standard manner.

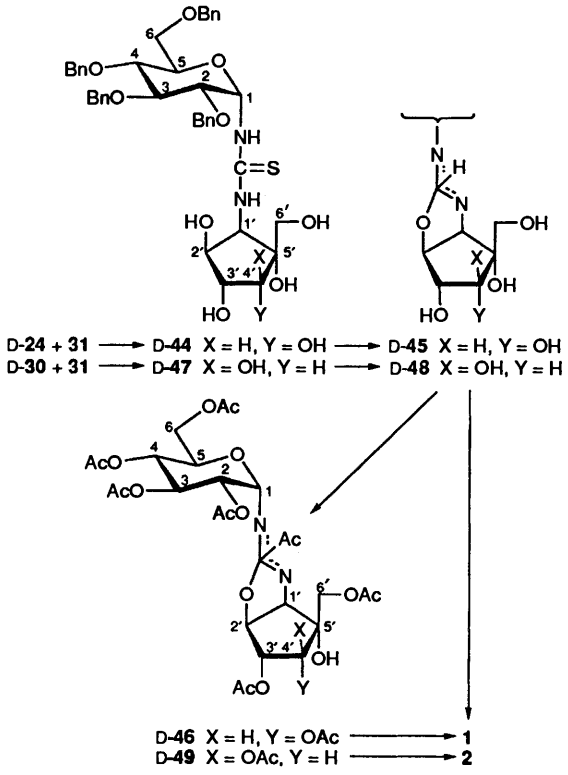
Treatment of the thiourea **32** with 9 mol equiv. of mercury(II) oxide in anhydrous diethyl ether at room temperature afforded, after 17 h, a quantitative yield of the isoureide **38** through conceivably simultaneous neighbouring group participation of the hydroxy function. Formation of other products was not observed in the reaction mixture by TLC even in the early stages of the reaction. Likewise, the thiourea **33** readily gave an isoureide **39** in good yield. On the other hand, under similar conditions, compound **34** gave an isoureido compound **40** with a six-membered ring in 66% yield after a rather prolonged reaction time (55 h). In this case, judging from the TLC analysis, a carbodiimide formed initially seemed to encounter an intramolecular attack of the hydroxy group. Some carbodiimides have been shown[17] to react with alkoxylates to give 2-alkylisoureas. On the other hand, similar treatment of the thiourea **35** with HgO gave only the carbodiimide **41** and an expected isoureido compound with a seven-membered ring was not obtained. Furthermore, the cyclohexylthiourea derivative **36** also readily underwent cyclisation to give a diastereoisomeric mixture of the isoureides **42a**, **b** in 91% yield. The structure of the isoureides **38**–**42** was deduced on the basis of ^1H NMR and IR spectra, and all compounds, except for compound **39**, are mixtures of interconvertible tautomers or single compounds, the structures of which are difficult to assign with respect to the position of the double bond of the isoureido ring. Therefore, the above studies clearly showed that an isoureido compound may be preferentially constructed from thiourea derivatives under mild conditions when a hydroxy group is situated in a position that satisfies a steric requirement for ring formation.

The thiourea **37** derived from a coupling of isothiocyanate **31** and 1,2-diaminoethane produced under similar conditions, a cyclic guanidine **43** in good yield.

These model experiments suggested that the isothiocyanate **31** reacts directly with the free branched-chain aminocyclopentanetetraols D-, L-**24** and D-, L-**30**, to give the thiourea derivatives which would simultaneously be converted into the



For convenience, the structures of compounds **42a**, **b** depict only one of the diastereoisomers



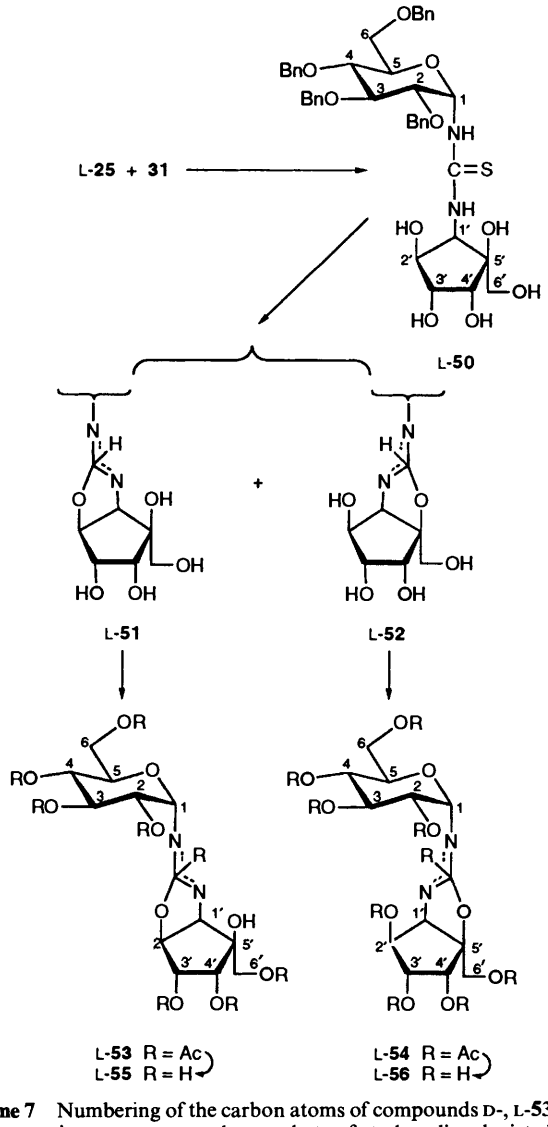
Scheme 6 Numbering of the carbons atoms of compounds D-, L-**45**, -**46**, -**48** and -**49**, for convenience, corresponds to that of trehazolin depicted by structure **2**

desired five-membered cyclic isoureido compounds *via* neighbouring group participation.

Synthesis of Compound **1** *and its Diastereoisomer.*—Coupling of the amines D- and L-**24** with 1.2 mol equiv. of the isothiocyanate **31** was carried out successfully in aq. 75% DMF for 4 h at room temperature to give the thioureas * D-and L-**44** in 91 and 86% yield, respectively. Treatment of D- and L-**44** with an excess of HgO in acetone–diethyl ether (1:6, v/v) for 23 h at room temperature resulted in formation of a dihydrooxazole ring to give the isoureas D- and L-**45** almost quantitatively. Deblocking of the benzyl ether groups of compounds D- and L-**45** was effected by treatment with sodium in liquid ammonia to afford, after chromatography on a column of Dowex 50W-X2 (H^+) resin with aq. ammonia as the eluent, pure compound **1** and its diastereoisomer **3**, respectively, which were further characterised as the octa-*N*,*O*-acetyl derivatives D- and L-**46**. The structures were supported by their IR and ^1H NMR (Tables 1 and 2) spectroscopic data. Removal of the *N*,*O*-acetyl groups of D- and L-**46** proceeded smoothly in methanol containing sodium methoxide to give compounds **1** and **3** quantitatively. The ^1H NMR spectroscopic data of compounds **1** and D-**46** were substantially similar to those reported for both authentic samples of trehalostatin [2] and trehazolin.[4] Therefore, it was rather difficult to distinguish between synthetic compound **1** and authentic trehalostatin by just comparing their ^1H NMR spectroscopic data measured under different conditions. Although their direct identification may be impossible because an authentic sample is not as yet available,† a final conclusion would properly be drawn from the biological properties of the synthetic compounds **1** and **3**.

Synthesis of Trehazolin and its Diastereoisomer.—Likewise, coupling of the amines D- and L-**30** with the isothiocyanate **31** afforded the thioureas D- (100%) and L-**47** (91%), respectively, which were similarly converted into the isoureides D- (92%) and L-**48** (93%). Likewise, deblocking of the benzyl groups of compounds D-, L-**48** afforded, after chromatography, trehazolin **2** and its diastereoisomer **4**. The corresponding octa-*N*,*O*-acetyl derivatives D- (77%) and L-**49** (80%) were also convertible into the deprotected parents **2** (100%) and **4** (76%) by treatment with methanolic sodium methoxide. The ^1H NMR spectra (Tables 1 and 2) supported their assigned structures.

Compounds **2** and **4** were then compared with authentic trehazolin mainly on the basis of ^1H NMR spectra data measured under similar conditions, and it was concluded that compound **2** was clearly identical with an authentic sample ‡ in all respects, thereby establishing the structure and absolute configuration of trehazolin as depicted in structure **2**.



Scheme 7 Numbering of the carbon atoms of compounds D-, L-**53**–**56**, for convenience, corresponds to that of trehazolin depicted by structure **2**

* The D-,L-notation of the compound-numbers **44**–**56** refers only to that of the absolute configuration of the cyclitol moiety.

† Dr. Nakayama, personal communication: An authentic sample of trehalostatin,[1,2] enough for unequivocal identification, is not yet available.

‡ The D-,L-notation of the compound-numbers **44**–**56** refers only to that of the absolute configuration of the cyclitol moiety.

Table 1 ^{1}H NMR spectroscopic data[a] (270 MHz; D_2O) of compounds **1–4** and D- and L-**56**

	Chemical shifts (δ_H)					
Proton	**1**	**2**	**3**	**4**	D-**56**	L-**56**
1-H	5.17	5.20	5.13	5.13	5.25	5.24
2-H	3.58	3.69–3.55	3.56	3.65–3.22	3.64–3.59	3.77–3.54
3-H	3.50	3.50	3.58–3.44	3.65–3.22	3.52	3.52
4-H	3.25	3.26	3.24	3.65–3.22	3.26	3.28
5-H	3.42	3.46–3.38	3.35	3.65–3.22	3.44	3.44
6-H_2	3.67, 3.58	3.69–3.55	3.58–3.44	3.65–3.22	3.68, 3.58	3.81
1′-H	4.25	4.21	4.19	4.15		
2′-H	4.85	4.80	4.78	4.73	3.99–3.90	
3′-H	4.06	4.06	4.00	3.98	3.78–3.74	3.99–3.92
4′-H	3.80	3.81	3.76	3.75		3.77–3.54
6′-H_2	3.66, 3.50	3.67, 3.57	3.58–3.44	3.65–3.22	3.79, 3.62	
	Coupling constants (Hz)					
J	**1**	**2**	**3**	**4**	D-**56**	L-**56**
$J_{1,2}$	5.1	5.5	5.1	4.4	4.8	5.1
$J_{2,3}$	8.8	9.9	9.4		8.4	8.8
$J_{3,4}$	9.9	9.2	8.6		9.0	9.1
$J_{4,5}$	9.5	9.5	10.1		9.3	9.3
$J_{5,6}$	2.7, 5.9		2.8, 3.2		2.9, 5.1	2.8, 4.7
$J_{6,6}$	13.0				11.1	12.8
$J_{1',2'}$	8.4	8.4	8.2	8.1		
$J_{2',3'}$	1.2	2.8	1.1	2.4		
$J_{3',4'}$	5.1	4.4	5.1	4.7		
$J_{6',6'}$	12.1	12.3			12.8	

[a] Chemical shifts (δ_H) are given relative to Me_2CO as reference. Numbering of the carbon atoms of trehalostatin **1** and D-, L-**56**, for convenience, corresponds to that of trehazolin **2**.[4]

Synthesis of Analogues of Trehazolin, the 4′,5′-Diepimer of Trehazolin.—In order to elucidate an inhibitory-activity and structure relationship for this kind of inhibitor, trehalostatin analogues in which the aminocyclitol parts were epimeric at C-5′ were prepared using the amino alcohols L- and D-**25**. In these amino alcohols, the amino functions possess two, secondary and tertiary, types of *cis*-β-hydroxy groups on the cyclopentane rings. Therefore, it would also be of interest to know if there is a stereochemical preference for the isoureido ring-formation.

On treatment with HgO, the glycosyl thiourea L-**50**, similarly obtained (90%) by coupling of substrates L-**25** and **31**, gave rise to an inseparable mixture of two isoureides L-**51** and L-**52**, these two, as expected, being isomeric with respect to a position on the isoureido ring. Deblocking of tetra ethers L-**51** and -**52** gave, after acetylation, the octa-*N*,*O*-acetyl L-**53** and the nona-*N*,*O*-acetyl derivatives L-**54**. Compound L-**53** was deacetylated with methanolic sodium methoxide or methanolic ammonia to give a 1:2–4 mixture of two trehazolin analogues L-**55** and L-**56**, the product ratio of which was estimated only on the basis of the ^{1}H NMR spectrum. Compound L-**55** could not be isolated pure, because it is readily interconvertible to the more stable isomer L-**56** under basic reaction conditions. Compound L-**56** was thus obtained practically pure from L-**54**.

Likewise, the analogue D-**56** was synthesised from the thiourea D-**50**, obtained from substrates D-**25** and **31**.

The structures of the per-*N*,*O*-acetyl derivatives of the cyclic isoureas, compounds **46**, **49**, **53** and **54**, with respect to the positions of the *N*-acetyl functions have not yet been established. Indeed, isolation of two octa-*N*,*O*-acetyl derivatives of trehalostatin has been reported and their structures were deduced on the basis of their ^{1}H NMR spectroscopic data.[3] However, we did not observe any formation of two such octa-*N*,*O*-acetates when either crude trehalostatin or crude trehazolin was acetylated in a similar manner. From consideration of their ^{1}H NMR spectroscopic data (Tables 1 and 2), the acetyl groups seem to be located on the nitrogen atoms of the isoureido rings, since the chemical shifts of the anomeric protons attached to C-1 of the free compounds remain essentially unchanged when the acetylated compounds are analysed.

Biological Assay.—The inhibitory activities of the synthesized six α-glucopyranosyl isoureido derivatives **1–4**, and D-, L-**56**, against silkworm and porcine trehalases were determined,* and the data are listed in Table 3. Trehazolin **2** showed very strong inhibitory activity as had been reported,[4] and, therefore, its whole structure was definitely assigned on both chemical and biochemical bases. Interestingly, the diastereoisomer **4** still possesses about one-third of the activity against silkworm trehalase and about one-tenth that against porcine trehalase. However, both synthetic compound **1** and its diastereoisomer **3** were found to lack any observable inhibitory activity, revealing that no naturally occurring inhibitor can have either structure **1** or structure **3**. Accordingly, the initial structure proposed[3] for trehalostatin was shown to be incorrect, and the present results suggested that trehalostatin should be identical with trehazolin.

It is interesting of note that, in contrast to the parent compounds **1** and **3**, their analogues D-, L-**56** both possess mild inhibitory activity against silkworm trehalase. These results might suggest that the configuration of the hydroxy functions of the branched-chain aminocyclitol moieties plays an important role in binding the active site of the enzymes: the cyclopentane rings possess envelope conformations having three hydroxy groups in *trans*-pseudoequatorial positions as in compounds

* Dr. Shuji Takahashi, personal communication.

Table 2 ^{1}H NMR spectroscopic data[a] (270 MHz; $CDCl_3$) of the octa-*N,O*-acetyl derivatives D-, L-**46**, D-, L-**49** and D-, L-**53**, and the nona-*N,O*-acetyl derivatives D-, L-**54**

	Chemical shifts (δ_H)							
Proton	D-**46**	L-**46**	D-**49**	L-**49**	D-**53**	L-**53**	D-**54**	L-**54**
1-H	5.58	5.88	5.59	5.53	5.64	5.57	5.60	5.57
2-H	5.06	5.12	5.07	5.09	5.03	5.05	5.07	5.11
3-H	5.40	5.42	5.40	5.54	5.45	5.47	5.49	5.43
4-H	5.07	5.08	5.08	5.09	5.08	5.09	5.12	5.11
5-H	4.30	4.28	4.31	4.27–4.17	4.33	4.28	4.31–4.25	4.33
6-H_2	4.22, 4.09	4.20, 4.11	4.20, 4.11	4.20, 4.09	4.22, 4.11	4.25, 4.09	4.06	4.23, 4.12
1′-H	4.97	5.04	4.90	4.90	4.85	4.85	4.94	4.96
2′-H	4.93	4.92	4.79	4.90	4.81	4.79		
3′-H	5.50	5.39	5.46	5.35	5.46	5.47	5.56	5.58
4′-H		5.33	5.55	5.50	5.34	5.37	5.38, 5.51	5.37, 5.47
6′-H_2	4.10, 3.95	4.16, 4.04	4.14, 3.91	4.25, 4.07	4.57, 4.35	4.59, 4.38	4.39, 4.17	4.31, 4.23
OH	3.58	3.30	3.77	3.90	3.91	3.76		
Ac	2.66, 2.14, 2.11, 2.10, 2.06, 2.03, 2.004, 2.002	2.64, 2.121, 2.115, 2.11, 2.09,[b] 2.04, 2.00, 1.99	2.66, 2.11,[b] 2.09, 2.08, 2.04, 2.00, 1.98	2.66, 2.10,[b] 2.09,[b] 2.06, 2.03, 2.00	2.66, 2.11, 2.095, 2.088, 2.06, 2.05, 2.04, 2.00	2.68, 2.105, 2.098, 2.08, 2.06, 2.03, 2.01, 1.91	2.63, 2.10, 2.09, 2.08, 2.05, 2.045, 2.038, 2.01, 1.95	2.59, 2.13, 2.12, 2.09[c] 2.04,[b] 2.00
	Coupling constants (Hz)							
J	D-**46**	L-**46**	D-**49**	L-**49**	D-**53**	L-**53**	D-**54**	L-**54**
$J_{1,2}$	4.0	4.0	4.4	4.0	4.4	4.4	4.0	4.3
$J_{2,3}$	10.3	9.9	10.3	10.0	10.3	9.9	9.9	10.3
$J_{3,4}$	9.7	9.7	9.5	10.0	9.8	9.5	9.5	9.5
$J_{4,5}$	9.9	9.5	10.3	10.0	9.5	10.3	9.2	9.5
$J_{5,6}$	1.8, 4.8	2.6, 4.4	2.2, 4.6	1.5, 4.4,	2.4, 4.4	2.0, 4.3	4.4	2.2, 3.7
$J_{6,6}$	12.5	12.6	12.5	9.9	12.2	12.7	13.9	12.3
$J_{1',2'}$	9.5	8.8	9.9		9.0	8.9	5.9	5.5
$J_{2',3'}$	3.7	2.6	3.3	1.5	3.2	3.7	5.3	4.0
$J_{3',4'}$	4.8	4.8	8.8	8.4	4.4	4.0	4.4	4.0
$J_{6',6'}$	11.7	11.7	11.7	12.1	12.9	12.8	12.6	12.5

[a] Chemical shifts (δ_H) are given relative to Me_4Si as reference. Numbering of the carbon atoms of all the compounds, for convenience, corresponds to that of trehazolin **2**.[4] [b] Peak of two acetoxy methyl groups. [c] Peak of three acetoxy methyl groups.

Table 3 Inhibitory activity of compounds **1**–**4**, and D- and L-**56**, against trehalases from silkworm and pig

	Inhibitory activity (IC_{50})/μg cm^{-3}	
Compound	Silkworm	Porcine
Compound **1**	> 100	*a*
Trehazolin **2**	0.016	0.0116
Diastereoisomer **3** of **1**	> 100	*a*
Trehazolin diastereoisomer **4**	0.45	0.0359
D-**56**	10	*a*
L-**56**	0.36	*a*

[a] Not measured.

2 and **4**. For further elucidation of the structure–activity relationship, attempted syntheses of several analogues related to trehazolin are in hand.

Experimental

M.p.s were determined on a MEL-TEMP capillary melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded for solutions in deuteriochloroform or dideuterium oxide with a JEOL JNM-EX 90 (90 MHz), JNM-GX 270 FT (270 MHz), or JNM-GX 400 FT (400 MHz) instrument, and *J*-values are given in Hz. IR spectra were measured with a JASCO A-202 or Hitachi FTS-65 spectrometer. TLC was performed on silica gel 60 F-254. (E. Merck, Darmstadt). The silica gel used for column chromatography was Wakogel C-300 (Wako Junyaku Kogyo Co., Osaka, Japan; 300 mesh) or silica gel 60 KO 70 (Katayama Kagaku Kogyo Co., Osaka, Japan). Organic solutions were dried over anhydrous Na_2SO_4 or $MgSO_4$, and concentrated at < 45 °C under diminished pressure.

The structures of newly prepared optically active compounds **17**–**26** (both D- and L-enantiomers) were confirmed by comparison of their ^{1}H NMR spectra with those of the corresponding racemates previously characterised.[5]

2,3-O-Cyclohexylidene Derivatives **6**, (±)-**7**, *and* **8** *of the Respective* (1,4/2,3,5)-, (1,2,3/4,5)-, *and* (1,4,5/2,3)-*5-Acetamido-1,4-di-O-acetylcyclopentane-1,2,3,4-tetraol.*—Preparation of the tri-*N,O*-acetyl compounds (±)-**7**, and **8** was carried out, starting from (±)-1,2-*O*-cyclohexylidene-*myo*-inositol (±)-**5**,[11] following essentially the procedure described by Angyal *et al.*[10] The nitro diols obtained were hydrogenated[12] in the presence of

Raney nickel T-4 and the products were, after conventional acetylation, separated by chromatography on a column of silica gel with acetone–toluene (1:2, v/v) as eluent to give the tri-*N,O*-acetyl compounds **6** (~40% overall yield), m.p. 143–144 °C (from benzene) (lit.,[12] 141.5–142 °C), (±)-**7** (~5%), m.p. 190–191 °C (from benzene) (lit.,[12] 186–188 °C), and **8** (~5%), m.p. 147–149 °C (from aq. EtOH) (lit.,[12] 150–151.5 °C).

2,3-O-*Cyclohexylidene Derivative* **8** *of* (±)-(1,4,5/2,3)-5-*Acetamido*-1,4-*di*-O-*acetylcyclopentane*-1,2,3,4-*tetraol*.—The penta-*N,O*-acetyl derivative **9**[5] (1.00 g, 2.78 mmol) derived from compound **6** was treated with 2 mol dm^{-3} HCl (20 cm^3) for 2 h at 80 °C. The reaction mixture was evaporated to afford a crystalline residue, which was *O*-cyclohexylidenated with 1,1-dimethoxycyclohexane (0.74 cm^3, 4.73 mmol) and a catalytic amount of toluene-*p*-sulfonic acid (PTSA) in DMF (20 cm^3) for 14 h at room temperature. After neutralisation with $NaHCO_3$, the mixture was treated with acetic anhydride and pyridine at room temperature, and chromatography of the product on a column of silica gel (30 g) with acetone–toluene (1:2, v/v) as eluent gave the *triacetyl compound* **8** (856 mg, 87%) as crystals.

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivative* L-**12** *of* 1L-(1,4,5/2,3)-5-*Acetamido*-1-O-[(1S)-O-*acetylmandelyl*]-*cyclopentane*-1,2,3,4-*tetraol and that,* D-**12**, *of the* 1D *Diastereoisomer*.—To a mixture of compound (±)-**11** (1.30 g, 4.16 mmol), 4-(dimethylamino)pyridine (DMAP) (101 mg, 0.83 mmol), and (*S*)-(+)-acetylmandelic acid (970 mg, 4.99 mmol) in CH_2Cl_2 (15 cm^3) was added a solution of DCC (1.03 g, 4.99 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C. After 15 min, hexane (50 cm^3) was added to the reaction mixture, which was filtered through a bed of Celite, and the filtrate was diluted with EtOAc (100 cm^3), washed successively with 1 mol dm^{-3} HCl (100 cm^3) and aq. saturated $NaHCO_3$ (100 cm^3), and dried. Removal of a solvent gave a syrupy residue, which was chromatographed on a column of silica gel (100 g) with butan-2-one–toluene (1:10, v/v) as eluent to give, first, the *acetylmandelate* L-**12** (789 mg, 39%) as a syrup (Found: C, 64.1; H, 6.7; N, 2.8. $C_{26}H_{33}NO_8$ requires C, 64.1; H, 6.8; N, 2.9%); $[\alpha]_D^{28}$ +68 (*c* 0.44, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O) and 1660 (NAc); δ_H(270 MHz; $CDCl_3$) 7.41 (5 H, s, Ph), 5.79 [1 H, s, Ph(AcO)C*H*CO], 5.18 (1 H, d, *J* 6.2, 1-H), 4.64 (2 H, s), 4.56–4.49 (2 H, m), 2.19 and 1.65 (each 3 H, 2 s, 2 × Ac), 1.65–1.25 (10 H, m, C_6H_{10}) and 1.55 and 1.47 (each 3 H, 2 s, CMe_2).

The second fraction gave the *acetylmandelate* D-**12** (855 mg, 42%) as a syrup (Found: C, 64.2; H, 6.5; N, 2.8%); $[\alpha]_D^{28}$ +11.2 (*c* 1.22, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O) and 1660 (NAc); δ_H(270 MHz; $CDCl_3$) 7.42–7.35 (5 H, m, Ph), 5.83 [1 H, s, Ph(AcO)C*H*CO], 5.37 (1 H, d, *J* 5.9, 1-H), 4.64–4.51 (3 H, m), 4.40 (1 H, d, *J* 5.5), 2.18 and 1.96 (each 3 H, 2 s, 2 × Ac), 1.78 and 1.54 (each 3 H, 2 s, CMe_2) and 1.75–1.34 (10 H, m, C_6H_{10}).

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivatives* D-*and* L-**11** *of the Respective* 1D- *and* 1L-(1,4,5/2,3)-5-*Acetamido*-*cyclopentane*-1,2,3,4-*tetraol*.—To a solution of compound D-**12** (789 mg, 1.62 mmol) in CH_2Cl_2 (15 cm^3) was added 1 mol dm^{-3} methanolic NaOMe (1.0 cm^3), and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with $CHCl_3$ (80 cm^3), and the solution was washed with water (50 cm^3 × 2) and dried. Removal of a solvent gave a syrupy residue, which was chromatographed on a column of silica gel (30 g) with acetone–toluene (1:4, v/v) to give the *alcohol* D-**11** (465 mg, 92%) as crystals, m.p. 185–187 °C (from EtOH) (Found: C, 62.0; H, 8.2; N, 4.4. $C_{16}H_{25}NO_5$ requires C, 61.7; H, 8.1; N, 4.5%); $[\alpha]_D^{29}$ +49.4 (*c* 1.18, $CHCl_3$).

Compound L-**12** (799 mg, 1.64 mmol) was similarly converted into the *alcohol* L-**11** (466 mg, 91%), m.p. 184–185 °C (from EtOH) (Found: C, 62.1; H, 8.3; N, 4.4%); $[\alpha]_D^{28}$ −44.5 (*c* 1.14, $CHCl_3$).

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivatives* D-*and* L-**13** *of the Respective* 1D- *and* 1L-(1,4,5/2,3)-5-*Acetamido*-1-O-(*methylthio*)*thiocarbonylcyclopentane*-1,2,3,4-*tetraol*.—A mixture of the alcohol D-**11** (93 mg, 0.30 mmol), 60% NaH (36 mg, 0.90 mmol), and THF (2 cm^3) was stirred for 20 min at room temperature. To the mixture were added CS_2 (0.19 cm^3, 3 mmol) and MeI (0.19 cm^3, 3 mmol), and the mixture was stirred for 20 min at room temperature, then was diluted with EtOAc (30 cm^3), washed with water (15 cm^3 × 2), and dried. Removal of a solvent gave a syrup, which was chromatographed on a column of silica gel (4 g) with butan-2-one–toluene (1:9, v/v) as eluent to give the *xanthate* D-**13** (120 mg, 100%) as a syrup (Found: C, 53.5; H, 6.5; N, 3.4. $C_{18}H_{27}NO_5S_2$ requires C, 53.8; H, 6.8; N, 3.5%); $[\alpha]_D^{28}$ −9.5 (*c* 1.54, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1660 (NAc); δ_H(270 MHz; $CDCl_3$) 6.25 (1 H, d, *J* 5.5, 1-H), 4.75–4.70 (2 H, m), 4.64 (1 H, dd, *J* 5.5 and 5.5), 4.58 (1 H, d, *J* 5.5), 2.60 (3 H, s, SMe), 2.06 (3 H, s, Ac), 1.79–1.30 (10 H, m, C_6H_{10}) and 1.75 and 1.30 (each 3 H, 2 s, CMe_2).

Compound L-**11** (81 mg, 0.26 mmol) was similarly converted into the *xanthate* L-**13** (99 mg, 95%) as a syrup (Found: C, 53.9; H, 6.5; N, 3.4%); $[\alpha]_D^{31}$ +8.1 (*c* 1.02, $CHCl_3$).

1,2-O-*Cyclohexylidene*-3,4-N,O-*isopropylidene Derivatives* D-*and* L-**14** *of the Respective* 1D- *and* 1L-(1,2/3,4)-4-*Acetamido*-*cyclopentane*-1,2,3-*triol*.—To a solution of the xanthate L-**13** (99 mg, 0.25 mmol) and a catalytic amount of AIBN (4 mg, 0.025 mmol) in toluene (2 cm^3) was added Bu_3SnH (130 mm^3, 0.49 mmol) under Ar. The mixture was stirred for 45 min under reflux, and was then diluted with EtOAc (30 cm^3), washed with water (10 cm^3 × 2), and dried. The solution was concentrated to give a residue, which was chromatographed on a column of silica gel (3 g) with butan-2-one–toluene (1:5, v/v) as eluent to give *compound* D-**14** (45 mg, 62%) as crystals, m.p. 146–150 °C (from butan-2-one–toluene) (Found: C, 65.4; H, 8.4; N, 4.7. $C_{16}H_{25}NO_4$ requires C, 65.1; H, 8.5; N, 4.7%); $[\alpha]_D^{30}$ +37 (*c* 1.15, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1650 (NAc); δ_H(270 MHz; $CDCl_3$) 4.82 (1 H, dd, *J* 4.8 and 5.3), 4.57 (1 H, d, *J* 5.3), 4.42–4.35 (2 H, m), 2.33 (1 H, dd, *J* 7.7, J_{gem} 14.3, 5-H), 2.09 (3 H, s, Ac), 1.81 (1 H, ddd, *J* 4.8 and 8.4, J_{gem} 14.3, 5-H) and 1.65–1.37 (16 H, m, CMe_2 and C_6H_{10}).

Compound D-**13** (120 mg, 0.30 mmol) was similarly converted into *compound* L-**14** (60 mg, 68%), m.p. 151–152 °C (from EtOH) (Found: C, 65.1; H, 8.6; N, 4.7%); $[\alpha]_D^{25}$ −40 (*c* 1.25, $CHCl_3$). The ^1H NMR and IR spectra were superposable on those of its enantiomer D-**14**.

1D- D-**15** *and* 1L-(1,2/3,4)-4-*Acetamido*-1,2,3-*tri*-O-*acetyl*-*cyclopentane*-1,2,3-*triol* L-**15**.—A mixture of compound D-**14** (45 mg, 0.15 mmol) and 2 mol dm^{-3} HCl (2 cm^3) was stirred for 5 h at 80 °C, and was then evaporated. The residue was acetylated conventionally and the product was chromatographed on a column of silica gel (2 g) with acetone–toluene (1:2, v/v) as eluent to give the *tetra*-N,O-*acetyl derivative* D-**15** (44 mg, 97%) as a syrup (Found: C, 51.6; H, 6.2; N, 4.6. $C_{13}H_{19}NO_7$ requires C, 51.8; H, 6.4; N, 4.7%); $[\alpha]_D^{31}$ +6.4 (*c* 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300 (NH), 1740 (OAc), 1650 (NAc) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 5.97 (1 H, br d, $J_{4,NH}$ 8.1, NH), 5.40–5.33 (1 H, m, 1-H), 5.30–5.23 (2 H, m, 2- and 3-H), 4.83–4.72 (1 H, m, 4-H), 2.30 (1 H, ddd, $J_{1,5}$ 2.9, $J_{4,5}$ 8.4, and J_{gem} 14.7, 5-H), 2.14–1.96 (1 H, m, 5-H) and 2.10, 2.061, 2.059 and 1.99 (each 3 H, 4 s, 4 × Ac).

Compound L-**14** (59 mg, 0.20 mmol) was similarly converted into *compound* L-**15** (54 mg, 90%) (Found: C, 51.6; H, 6.1; N, 4.6%); $[\alpha]_D^{24}$ −3.3 (*c* 1.29, $CHCl_3$).

(2S)-2-*Acetamido*-1,4-*diacetoxybutane* (S)-**16**.—(*a*) The tetra-acetate D-**15** (44 mg, 0.14 mmol) was treated with NaOMe in MeOH (1 cm^3) at room temperature. The reaction mixture was neutralised with Amberlite IR 120B (H^+) resin and was then evaporated to give a syrupy residue (24 mg), which was successively oxidised with aq. $NaIO_4$ (117 mg, 0.55 mmol in 1 cm^3) at room temperature. After neutralisation with $NaHCO_3$, the mixture was saturated with NaCl and was then extracted with tetrahydrofuran (THF) (20 cm^3 × 4). The extracts were dried over $MgSO_4$ and then evaporated to give a syrupy residue. The residue was reduced with $NaBH_4$ (52 mg, 1.36 mmol) in MeOH (2 cm^3) at room temperature. After neutralisation with AcOH, the mixture was evaporated to give a residue, which was acetylated conventionally. Chromatography of the product on a column of silica gel (1 g) with acetone–toluene (1:2, v/v) as eluent gave the *tri*-N,O-*acetyl aminobutanediol* (S)-**16** (18 mg, 57%) as needles, m.p. 120–121 °C (from EtOH) (Found: C, 51.6; H, 7.4; N, 5.9. $C_{10}H_{17}NO_5$ requires C, 51.9; H, 7.4; N, 6.1%); $[\alpha]_D^{29}$ −43 (*c* 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300 (NH), 1740 (OAc) and 1650 (NAc); δ_H(270 MHz; $CDCl_3$) 5.63 (1 H, br d, $J_{2,NH}$ 7.7, NH), 4.38–4.25 (1 H, m, 2-H), 4.22–4.04 (4 H, m, 1- and 4-H_2), 2.09, 2.06 and 2.00 (each 3 H, 3 s, 3 × Ac) and 1.97–1.73 (2 H, m, 3-H_2).

(*b*) L-Aspartic acid diethyl ester[13] (511 mg, 2.70 mmol) was treated with $LiAlH_4$ (350 mg, 9.22 mmol) in diethyl ether (5 cm^3) for 1 h at room temperature. Water (1 cm^3), aq. 15% NaOH (3 cm^3), and aq. 50% acetone (5 cm^3) were added in turn to the mixture, which was then filtered through a bed of Celite. The filtrate was neutralised with AcOH and evaporated. The residue was acetylated conventionally and the product was chromatographed on a column of silica gel (20 g) with acetone–toluene (1:3, v/v) as eluent to give the *tri*-N,O-*acetyl derivative* (*S*)-**16** (354 mg, 55%) as needles, m.p. 124–125 °C (from EtOH) (Found: C, 51.9; H, 7.2; N, 6.0%); $[\alpha]_D^{32}$ −42 (*c* 1.06, $CHCl_3$). It was identical with the compound derived from D-**15** on the basis of the ^1H NMR and IR spectra.

(2R)-2-*Acetamido*-1,4-*diacetoxybutane* (R)-**16**.—Compound L-**15** (54 mg, 0.18 mmol) was converted, as in the preparation of (*S*)-**16** from D-**15**, into the *tri*-N,O-*acetyl* (R)-**16** (25 mg, 66%), m.p. 118–119 °C (from EtOH) (Found: C, 51.5; H, 7.0; N, 6.0%); $[\alpha]_D^{25}$ +42 (*c* 1.14, $CHCl_3$). The ^1H NMR and IR spectra were superposable on those of its enantiomer (*S*)-**16**.

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivative* (±)-**17** *of* (±)-(1,2,3/4,5)-5-*Acetamidocyclopentane*-1,2,3,4-*tetraol*.—Compound (±)-**7** (1.28 g, 3.61 mmol) was de-*O*-acetylated conventionally with methanolic NaOMe in MeOH at room temperature. Without purification, the crude intermediate diol was treated with 2,2-dimethoxypropane (2 cm^3, 15.95 mmol) and a catalytic amount of PTSA in DMF (15 cm^3) for 4 h at 50 °C. After neutralisation with $NaHCO_3$, the reaction mixture was concentrated and the residue was treated with a solution of AcOH (0.5 cm^3) in MeOH (20 cm^3) for 48 h at room temperature. The mixture was evaporated and the residue was chromatographed on a column of silica gel (30 g) with acetone–toluene (1:4, v/v) to give the *alcohol* (±)-**17** (843 mg, 75%) as crystals, m.p. 146–147 °C (from toluene) (Found: C, 61.7; H, 7.9; N, 4.5. $C_{16}H_{25}NO_5$ requires C, 61.7; H, 8.1; N, 4.5%); ν_{max}(neat)/cm^{-1} 3300 (OH) and 1630 (NAc); δ_H(270 MHz; $CDCl_3$) 4.73 (1 H, dd, $J_{1,5}$ 5.1, $J_{4,5}$ 5.5, 5-H), 4.60 (1 H, d, 1-H), 4.38 (1 H, d, $J_{2,3}$ 4.6, 2-H), 4.15 (1 H, dd, $J_{3,4}$ 6.2, 3-H), 4.08 (1 H, ddd, $J_{4,OH}$ 8.4, 4-H), 2.85 (1 H, d, OH), 2.26 (3 H, s, Ac), 1.69–1.42 (10 H, m, C_6H_{10}) and 1.64 and 1.52 (each 3 H, 2 s, CMe_2).

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivatives* D- *and* L-**18** *of the Respective* 1D- *and* 1L-(1,2,3/4,5)-5-*Acetamido*-1-O-[(1S)-O-*acetylmandelyl*]*cyclopentane*-1,2,3,4-*tetraol*.—To a solution of the alcohol (±)-**17** (485 mg, 1.56 mmol), (*S*)-*O*-acetylmandelic acid (393 mg, 2.02 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (8 cm^3) was added a solution of DCC (406 mg, 2.02 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C, and the mixture was stirred for 0.5 h at 0 °C. The mixture was diluted with hexane (20 cm^3) at 0 °C and was then filtered through a bed of Celite. The filtrate was then diluted with EtOAc (20 cm^3), and the solution was washed successively with 1 mol dm^{-3} HCl (30 cm^3) and saturated aq. $NaHCO_3$ (30 cm^3), dried, and evaporated. The residue was chromatographed on a column of silica gel (80 g) with butan-2-one–toluene (1:4, v/v) as eluent to give, first, the 1L-(S)-*acetylmandelate* L-**18** (380 mg, 50%) as a syrup (Found: C, 63.8; H, 6.8; N, 2.9. $C_{26}H_{33}NO_8$ requires C, 64.1; H, 6.8; N, 2.9%); $[\alpha]_D^{21}$ +114 (*c* 1.29, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O) and 1660 (NAc); δ_H(270 MHz; $CDCl_3$) 7.49–7.38 (5 H, m, Ph), 6.11 [1 H, s, Ph(AcO)C*H*CO], 4.94 (1 H, dd, $J_{1,5}$ 5.5, $J_{4,5}$ 5.1, 5-H), 4.85–4.80 (1 H, m, 1-H), 4.58 (1 H, d, 4-H), 4.38–4.36 (2 H, m, 2- and 3-H), 2.19 and 1.43 (each 3 H, 2 s, 2 × Ac), 1.77–1.30 (10 H, m, C_6H_{10}) and 1.59 and 1.47 (each 3 H, 2 s, CMe_2).

The second fraction gave 1D-(S)-*acetylmandelate* D-**18** (364 mg, 48%) as crystals, m.p. 146–147 °C (from toluene) (Found: C, 64.1; H, 6.8; N, 2.9%); $[\alpha]_D^{21}$ −31.2 (*c* 1.16, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (C=O) and 1660 (NAc); δ_H(270 MHz; $CDCl_3$) 7.53–7.35 (5 H, m, Ph), 5.98 [1 H, s, Ph(AcO)C*H*CO], 4.93 (1 H, dd, $J_{1,2}$ 7.0, $J_{1,5}$ 4.9, 1-H), 4.82 (1 H, dd, $J_{4,5}$ 5.3, 5-H), 4.52 (1 H, d, 4-H), 4.46 (1 H, dd, $J_{2,3}$ 5.1, 2-H), 4.33 (1 H, d, 3-H), 2.20 and 2.14 (each 3 H, 2 s, 2 × Ac), 1.65 and 1.52 (each 3 H, 2 s, CMe_2) and 1.60–1.25 (10 H, m, C_6H_{10}).

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivatives* D- *and* L-**17** *of the Respective* 1D- *and* 1L-(1,2,3/4,5)-5-*Acetamidocyclopentane*-1,2,3,4-*tetraol*.—Conventional de-*O*-acylation of compound D-**18** (364 mg, 0.75 mmol) with methanolic NaOMe at room temperature gave a crystalline residue, which was chromatographed on a column of silica gel (12 g) with acetone–toluene (1:4, v/v) as eluent to afford the *alcohol* D-**17** (230 mg, 99%), m.p. 165–166 °C (from toluene) (Found: C, 61.8; H, 8.0; N, 4.4. $C_{16}H_{25}NO_5$ requires C, 61.7; H, 8.1; N, 4.5%); $[\alpha]_D^{19}$ −39 (*c* 0.97, $CHCl_3$).

Compound L-**18** (380 mg, 0.78 mmol) was similarly treated with methanolic NaOMe and the product was purified to give the *alcohol* L-**17** (221 mg, 91%), m.p. 165–166 °C (from toluene) (Found: C, 61.7; H, 8.0; N, 4.5%); $[\alpha]_D^{19}$ +41 (*c* 0.91, $CHCl_3$).

The ^1H NMR spectra of alcohols D- and L-**17** were identical with that of racemate (±)-**17**.

2,3-O-*Cyclohexylidene*-4,5-O-*isopropylidene Derivative* D-**19** *of* 2D-(2,3/4,5)-5-*Acetamido*-2,3,4-*trihydroxycyclopentanone*.—Compound L-**11** (465 mg, 1.49 mmol) was converted, as in the preparation of the racemate,[5] into the *ketone* D-**19** (399 mg, 87%) as plates, m.p. 128–129 °C (from EtOH) (Found: C, 62.1; H, 7.4; N, 4.4. $C_{16}H_{23}NO_5$ requires C, 62.1; H, 7.5; N, 4.5%); $[\alpha]_D^{21}$ +15.7 (*c* 0.94, $CHCl_3$).

Compound D-**17** (226 mg, 0.72 mmol) was oxidised with PCC (469 mg, 2.17 mmol) and molecular sieves 4 Å (450 mg) in CH_2Cl_2 (5 cm^3) for 2 h at room temperature. Silica gel column chromatography (20 g) of the crude product with diethyl ether as eluent gave the ketone D-**19** (219 mg, 98%), identical with the product obtained from compound L-**11**.

2,3-O-*Cyclohexylidene*-4,5-N,O-*isopropylidene Derivative* L-**19** *of* 2L-(2,3/4,5)-5-*Acetamido*-2,3,4-*trihydroxycyclopentanone*.—Compound D-**11** (466 mg, 1.50 mmol) was similarly converted into the *ketone* L-**19** (419 mg, 91%), m.p. 132–133 °C (from EtOH) (Found: C, 62.1; H, 7.3; N, 4.5%); $[\alpha]_D^{19}$ −14.7 (*c* 3.83, $CHCl_3$).

Compound L-**17** (213 mg, 0.68 mmol) was similarly oxidised

with PCC to give the ketone L-**19** (212 mg, 100%), identical with the product obtained from compound D-**11**.

1,2-O-*Cyclohexylidene*-3,4-N,O-*isopropylidene Derivatives* D- *and* L-**20** *of the Respective* 1D- *and* 1L-(1,2/3,4)-4-*Acetamido*-5-*methylenecyclopentane*-1,2,3-*triol and* 2,3-O-*Cyclohexylidene Derivatives* D- *and* L-**21** *of the Respective* (4R,5R)-*and* (4S,5S)-2-*Acetamido*-4,5-*dihydroxycyclopent*-2-*enone*.—The ketone D-**19** (399 mg, 1.29 mmol) was epoxidised, as in the preparation of the racemate,[5] with CH_2N_2 in dimethyl sulfoxide (DMSO)–diethyl ether and then the epoxides were treated with $P(OMe)_3$ in a sealed tube at 130 °C. The products were chromatographed on a column of silica gel (20 g) with acetone–hexane (1:7, v/v) as eluent to give, first, the *exo-olefin* D-**20** (180 mg, 45% overall yield) as crystals, m.p. 154–155 °C (from EtOH) (Found: C, 66.3; H, 8.1; N, 4.6. $C_{17}H_{25}NO_4$ requires C, 66.4; H, 8.2; N, 4.6%); $[\alpha]_D^{29}$ −10.3 (*c* 1.32, $CHCl_3$).

The second fraction gave the *enone* D-**21** (37 mg, 11% overall yield), m.p. 145–148 °C (from EtOH) (Found: C, 62.4; H, 7.0; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.1; H, 6.8; N, 5.6%); $[\alpha]_D^{27}$ +110 (*c* 1.77, $CHCl_3$).

The ketone L-**19** (410 mg, 1.33 mmol) was similarly treated with CH_2N_2 and the products were separated by chromatography. The first fraction gave the *exo-olefin* L-**20** (182 mg, 45% overall yield), m.p. 154–155 °C (from EtOH) (Found: C, 66.1; H, 8.2; N, 4.5%); $[\alpha]_D^{26}$ +15.3 (*c* 1.08, $CHCl_3$).

The second fraction gave the *enone* L-**21** (42 mg, 13%), m.p. 145–146 °C (from EtOH) (Found: C, 62.4; H, 6.9; N, 5.6%); $[\alpha]_D^{24}$ −124 (*c* 0.63, $CHCl_3$).

1D-(1,2,3/4,5)-D-**22** *and* 1L-(1,4,5/2,3)-5-*Acetamido*-1-C-*acetoxymethyl*-2,3,4-*tri*-O-*acetylcyclopentane*-1,2,3,4-*tetraol* L-**23**.—The exo-olefin L-**20** (226 mg, 0.74 mmol) was successively hydroxylated with OsO_4, as in the preparation of the racemate,[5] hydrolysed with 2 mol dm^{-3} HCl, and acetylated with acetic anhydride in pyridine. The products were chromatographed on a column of silica gel (5 g) with acetonitrile–toluene (2:3, v/v) as eluent to give, first, the *penta*-N,O-*acetyl derivative* D-**22** (154 mg, 49%) as a syrup (Found: C, 49.4; H, 5.7; N, 3.5. $C_{16}H_{23}NO_{10}$ requires C, 49.4; H, 6.0; N, 3.6%); $[\alpha]_D^{24}$ −11.6 (*c* 1.04, $CHCl_3$).

The second fraction gave the *penta*-N,O-*acetyl derivative* L-**23** (162 mg, 51%) as a syrup (Found: C, 49.0; H, 5.7; N, 3.6%); $[\alpha]_D^{24}$ −1.8 (*c* 0.90, $CHCl_3$).

1L-(1,2,3/4,5)- L-**22** *and* 1D-(1,4,5/2,3)-5-*Acetamido*-1-C-*acetoxymethyl*-2,3,4-*tri*-O-*acetylcyclopentane*-1,2,3,4-*tetraol* D-**23**.—Compound L-**20** (238 mg, 0.78 mmol) was similarly hydroxylated and the products were separated to give, first, the *penta*-N,O-*acetyl derivative* L-**22** (134 mg, 44%) as a syrup (Found: C, 49.0; H, 5.8; N, 3.5%); $[\alpha]_D^{24}$ +14.7 (*c* 0.87, $CHCl_3$).

The second fraction gave the *penta*-N,O-*acetyl derivative* D-**23** (187 mg, 56%) as a syrup (Found: C, 49.5; H, 5.8; N, 3.5%); $[\alpha]_D^{24}$ +5.9 (*c* 0.76, $CHCl_3$).

1D- D-**24** *and* 1L-(1,2,3/4,5)-5-*Amino*-1-C-(*hydroxymethyl*)-*cyclopentane*-1,2,3,4-*tetraol* L-**24**.—A mixture of the penta-N,O-acetyl derivative D-**22** (137 mg, 0.35 mmol) and 2 mol dm^{-3} hydrochloric acid (3 cm^3) was stirred for 3 h at 80 °C, and was then evaporated. The residue was chromatographed on a column of Dowex 50W X2 (H^+) resin (6 cm^3) with aq. 5% ammonia as eluent to give the *amino alcohol* D-**24** (60 mg, 95%) as a syrup, $[\alpha]_D^{23}$ −10.2 (*c* 0.83, water); ν_{max}(neat)/cm^{-1} 3350 (OH and NH_2); δ_H(270 MHz; D_2O) 3.98 (1 H, dd, $J_{3,4}$ 5.4, $J_{4,5}$ 5.6, 4-H), 3.89 (1 H, dd, $J_{2,3}$ 6.0, 3-H), 3.83 (1 H, d, 2-H), 3.55 and 3.45 (each 1 H, ABq, J_{gem} 11.9, 6-H) and 3.20 (1 H, d, 5-H).

The penta-*N,O*-acetyl compound L-**22** (123 mg, 0.32 mmol) was similarly converted into the amino alcohol L-**24** (60 mg, 100%) as a syrup, $[\alpha]_D^{22}$ +9.2 (*c* 0.99, water). The ^1H NMR and IR spectra were superposable on those of the enantiomer.

1D- D-**25** *and* 1L-(1,4,5/2,3)-5-*Amino*-1-C-(*hydroxymethyl*)-*cyclopentane*-1,2,3,4-*tetraol* L-**25**.—The penta-*N,O*-acetyl compound D-**23** (120 mg, 0.31 mmol) was similarly converted into the *amino alcohol* D-**25** (55 mg, 99%) as a syrup, $[\alpha]_D^{22}$ +9.2 (*c* 1.18, water); ν_{max}(neat)/cm^{-1} 3350 (OH and NH_2); δ_H(270 MHz; D_2O) 3.98 (1 H, dd, $J_{2,3}$ 4.8, $J_{3,4}$ 4.8, 3-H), 3.90 (1 H, dd, $J_{4,5}$ 7.5, 4-H), 3.86 (1 H, d, 2-H), 3.62 and 3.48 (each 1 H, ABq, J_{gem} 11.9, 6-H) and 3.13 (1 H, d, 5-H).

The penta-*N,O*-acetyl compound L-**23** (111 mg, 0.28 mmol) was similarly converted into the *amino alcohol* L-**25** (46 mg, 91%) as a syrup, $[\alpha]_D^{23}$ −6.8 (*c* 1.19, water).

1D- D-**26** *and* 1L-(1,2/3,4)-4-*Acetamido*-2,3-*di*-O-*acetyl*-5-*methylene*-1-O-*methylsulfonylcyclopentane*-1,2,3-*triol* L-**26**.—The exo-olefin D-**20** (176 mg, 0.57 mmol) was converted, as in the preparation of the racemate,[5] into the *mesyl ester* D-**26** (136 mg, 68%) as a syrup (Found: C, 44.5; H, 5.3; N, 3.9. $C_{13}H_{19}NO_8S$ requires C, 44.7; H, 5.5; N, 4.0%); $[\alpha]_D^{28}$ −14.4 (*c* 1.81, $CHCl_3$).

The exo-olefin L-**20** (172 mg, 0.56 mmol) was similarly converted into the *mesyl ester* L-**26** (152 mg, 78%) as a syrup (Found: C, 44.4; H, 5.3; N, 4.0%); $[\alpha]_D^{27}$ +14.8 (*c* 1.49, $CHCl_3$).

1D- D-**27** *and* 1L-(1,3,4/2)-4-*Acetamido*-1,2,3-*tri*-O-*acetyl*-5-*methylenecyclopentane*-1,2,3-*triol* L-**27**.—The mesyl ester L-**26** (152 mg, 0.44 mmol) was converted, as in the preparation of the racemate,[5] into the *tetra*-N,O-*acetyl compound* D-**27** (120 mg, 88%) as a syrup (Found: C, 53.4; H, 6.0; N, 4.6. $C_{14}H_{19}NO_7$ requires C, 53.7; H, 6.1; N, 4.5%); $[\alpha]_D^{25}$ +28.3 (*c* 2.28, $CHCl_3$).

The mesyl ester D-**26** (136 mg, 0.39 mmol) was similarly converted into the *tetra*-N,O-*acetyl compound* L-**27** (80 mg, 66%) as a syrup (Found: C, 53.5; H, 5.9; N, 4.4%); $[\alpha]_D^{28}$ −33.5 (*c* 1.46, $CHCl_3$).

1D-(1,3/2,4,5)- D-**28** *and* 1L-(1,2,4,5/3)-5-*Acetamido*-2,3,4-*tri*-O-*acetyl*-1-C-(*acetoxymethyl*)*cyclopentane*-1,2,3,4-*tetraol* L-**29**.—The exo-olefin L-**27** (80 mg, 0.26 mmol) was hydroxylated with OsO_4, as in the preparation of the racemate,[5] followed by conventional acetylation, and the products were chromatographed on a column of silica gel (7 g) with acetone–toluene (1:2, v/v) as eluent to give, first, the *penta*-N,O-*acetyl derivative* D-**28** (86 mg, 87%) as crystals, m.p. 145–146 °C (from EtOH) (Found: C, 49.1; H, 5.8; N, 3.6. $C_{16}H_{23}NO_{10}$ requires C, 49.4; H, 6.0; N, 3.6%); $[\alpha]_D^{31}$ +3.8 (*c* 0.72, $CHCl_3$).

The second fraction gave the *penta*-N,O-*acetyl derivative* L-**29** (13 mg, 13%) as a syrup (Found: C, 49.1; H, 5.7; N, 3.6%); $[\alpha]_D^{30}$ −11.1 (*c* 0.66, $CHCl_3$).

1L-(1,3/2,4,5)- L-**28** *and* 1D-(1,2,4,5/3)-5-*Acetamido*-2,3,4-*tri*-O-*acetyl*-1-C-(*acetoxymethyl*)*cyclopentane*-1,2,3,4-*tetraol* D-**29**.—The exo-olefin D-**27** (92 mg, 0.29 mmol) was similarly hydroxylated and separated to give the *penta*-N,O-*acetyl derivative* L-**28** (97 mg, 85%) as crystals, m.p. 144–145 °C (from EtOH) (Found: C, 49.0; H, 5.8; N, 3.6%); $[\alpha]_D^{21}$ −3.9 (*c* 1.27, $CHCl_3$), and the *penta*-N,O-*acetyl derivative* D-**29** (17 mg, 15%) as a syrup (Found: C, 49.1; H, 5.7; N, 3.5%); $[\alpha]_D^{21}$ +12.2 (*c* 1.72, $CHCl_3$).

1D- D-**30** *and* 1L-(1,3/2,4,5)-5-*Amino*-1-C-(*hydroxymethyl*)-*cyclopentane*-1,2,3,4-*tetraol* L-**30**.—The penta-*N,O*-acetyl compound D-**28** (86 mg, 0.22 mmol) was treated with 2 mol dm^{-3} HCl (2 cm^3) for 4.5 h at 80 °C. The product was purified on a column of Dowex 50W X2 (H^+) resin (4 cm^3) with aq. 5%

NH_3 to give the *amino alcohol* D-**30** (37 mg, 94%) as a syrup, $[\alpha]_D^{30}$ +5.3 (*c* 1.84, water); ν_{max}(neat)/cm^{-1} 3350 (OH and NH_2); δ_H(270 MHz; D_2O) 3.93–3.46 (5 H, m, 2-, 3-, 4- and 6-H) and 3.06 (1 H br d, $J_{4,5}$ 6.2, 5-H).

Similar treatment of the penta-*N,O*-acetyl derivative L-**28** (93 mg, 0.24 mmol) gave the *amino alcohol* L-**30** (45 mg, 100%) as a syrup, $[\alpha]_D^{21}$ −2.8 (*c* 2.15, water). The ^{1}H NMR and IR spectra were superposable on those of the enantiomer.

N-(2-*Hydroxyethyl*)-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **32**.—A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl isothiocyanate[16] **31** (74 mg, 0.13 mmol) and 2-aminoethanol (10 mm^3, 0.17 mmol) in CH_2Cl_2–MeOH (1.5 cm^3; 2:1, v/v) was stirred for 2.5 h at room temperature. Removal of solvent gave a syrupy residue, which was chromatographed on a column of silica gel (2 g) with EtOAc–toluene (1:2, v/v) as eluent to give the *thiourea* **32** (76 mg, 93%) as a syrup (Found: C, 68.8; H, 6.6; N, 4.2. $C_{37}H_{42}N_2O_6S$ requires C, 69.1; H, 6.6; N, 4.4%); $[\alpha]_D^{25}$ +118.5 (*c* 2.12, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3330 (OH and NH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.47 (1 H, br dd, $J_{1,NH}$ 4.6 and 4.6, NH), 7.37–7.10 (20 H, m, 4 × Ph), 6.58 (1 H, br s, N′H), 5.09 (1 H, d, $J_{1',2'}$ 4.4, 1′-H), 4.90 and 4.77 (each 1 H, ABq, J_{gem} 10.8, PhCH_2), 4.80 and 4.55 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.67 and 4.62 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.49 and 4.42 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 3.90–3.33 (10 H, m, 2′-, 3′-, 4′- and 5′-H and 1, 2- and 6′-H_2) and 2.43 (1 H, br s, OH).

N-(2-*Hydroxyethyl*)-N-*methyl*-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **33**.—A mixture of the isothiocyanate **31** (111 mg, 0.19 mmol) and *N*-methylethanolamine (31 mm^3, 0.38 mmol) in CH_2Cl_2–MeOH (3 cm^3; 2:1, v/v) was stirred for 2 h at room temperature, and was then evaporated to give a syrupy residue. The residue was purified by a column of silica gel (5 g) with EtOAc–toluene (1:4, v/v) as eluent to afford the *thiourea* **33** (122 mg, 98%) as a syrup (Found: C, 69.1; H, 7.00; N, 4.2. $C_{38}H_{44}N_2O_6S$ requires C, 69.5; H, 6.8; N, 4.3%); $[\alpha]_D^{20}$ +21.3 (*c* 1.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 and 3250 (NH and OH) and 1570 (NH); δ_H(270 MHz; $CDCl_3$) 7.56 (1 H, br s, N′H), 7.34–7.12 (20 H, m, 4 × Ph), 6.44 (1 H, dd, $J_{1',2'}$ 5.5, $J_{1,N'H}$ 6.2, 1′-H), 4.93–4.47 (8 H, m, 4 × PhCH_2), 3.87 (1 H, dd, $J_{1,2}$ 5.5, $J_{2',3'}$ 9.2, 2′-H), 3.81–3.52 (9 H, m, 3′-, 4′- and 5′-H, 6′-H_2, and CH_2CH_2), 3.26 (3 H, s, NMe) and 2.42 (1 H, br s, OH).

N-(3-*Hydroxypropyl*)-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **34**.—To a solution of the isothiocyanate **31** (60 mg, 0.10 mmol) in CH_2Cl_2–MeOH (1.5 cm^3; 2:1, v/v) was added 3-aminopropan-1-ol (16 mm^3, 0.21 mmol) and the mixture was stirred for 2 h at room temperature. Evaporation of solvent gave a syrupy residue, which was chromatographed on a column of silica gel (3 g) with acetone–toluene (1:5, v/v) as eluent to afford the *thiourea* **34** (69 mg, 100%) as a syrup (Found: C, 69.4; H, 6.7; N, 4.2%); $[\alpha]_D^{21}$ +124 (*c* 1.49, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3320 (NH and OH) and 1550 (NH); δ_H(270 MHz; $CDCl_3$) 7.58 (1 H, br dd, $J_{1,NH}$ 4.0 and 4.0, NH), 7.36–7.12 (20 H, m, 4 × Ph), 6.52 (1 H, br s, N′H), 5.03 (1 H, br d, $J_{1',2'}$ 5.1, 1′-H), 4.90 and 4.77 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.81 and 4.46 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.67 and 4.61 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.46 and 4.40 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 3.91–3.29 (9 H, m, 3′-, 4′- and 5′-H, 1- and 6′-H_2), 3.65 (1 H, dd, $J_{1',2'}$ 5.1, $J_{2',3'}$ 9.9, 2-H), 3.04 (1 H, dd, $J_{3',OH}$ 5.9 and 6.2, OH) and 1.54–1.50 (2 H, m, 2-H_2).

N-(4-*Hydroxybutyl*)-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **35**.—A mixture of the isothiocyanate **31** (56 mg, 0.097 mmol) and 4-aminobutan-1-ol (14 mm^3, 0.15 mmol) in CH_2Cl_2–MeOH (1.5 cm^3; 2:1, v/v) was stirred for 2 h at room temperature. Removal of solvent gave a syrupy residue, which was chromatographed on a column of silica gel (2 g) with acetone–toluene (1:6, v/v) as eluent to give the *thiourea* **35** (62 mg, 95%) as a syrup (Found: C, 69.4; H, 6.6; N, 4.2. $C_{39}H_{46}N_2O_6S$ requires C, 69.8; H, 6.9; N, 4.2%); $[\alpha]_D^{21}$ +111 (*c* 1.47, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3320 (NH and OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.36–7.12 (21 H, m, 4 × Ph and NH), 6.50 (1 H, br s, N′H), 5.01 (1 H, br d, $J_{1',2'}$ 4.9, 1′-H), 4.89 and 4.77 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.81 and 4.46 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.68 and 4.62 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.49 and 4.41 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 3.87 (1 H, ddd, $J_{4',5'}$ 9.5, $J_{5',6'}$ 1.5 and 6.0, 5′-H), 3.77 (1 H, dd, $J_{2',3'}$ 9.2, $J_{3',4'}$ 9.2, 3′-H), 3.66 (1 H, dd, $J_{1,2}$ 4.9, $J_{2,3}$ 9.2, 2-H), 3.61–3.45 (6 H, m, 1-, 4- and 6′-H_2), 3.40 (1 H, dd, $J_{3',4'}$ 9.2, $J_{4',5'}$ 9.5, 4′-H), 1.78 (br s, 1 H, OH) and 1.61–1.43 (4 H, m, 2- and 3-H_2).

N-[(1,2,6/0)-2,6-*Dihydroxycyclohexyl*]-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **36**.—A mixture of the isothiocyanate **31** (112 mg, 0.19 mmol) and (1,2,3/0)-2-aminocyclohexane-1,3-diol[14] (20 mg, 0.15 mmol) in DMF (2 cm^3) was stirred for 4 h at room temperature. Evaporation of solvent gave a syrupy residue, which was purified on a column of silica gel (5 g) with EtOH–toluene (1:10, v/v) as eluent to afford the *thiourea* **36** (102 mg, 93%) as a syrup (Found: C, 68.8; H, 6.7; N, 3.9. $C_{41}H_{48}N_2O_7S$ requires C, 69.1; H, 6.8; N, 3.9%); $[\alpha]_D^{23}$ +116 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (NH and OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.84 (1 H, d, $J_{1,NH}$ 8.4, NH), 7.36–7.08 (20 H, m, 4 × Ph), 6.61 (1 H, d, $J_{1',N'H}$ 1.8, N′H), 5.22 (1 H, dd, $J_{1',2'}$ 5.0, $J_{1',N'H}$ 1.8, 1′-H), 4.91 and 4.77 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.79 and 4.43 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.66 and 4.46 (each 2 H, 2 s, 2 × PhCH_2), 4.32 (1 H, br d, $J_{1,NH}$ 8.4, 1-H), 4.07 (1 H, br s, 2- or 6-H), 3.96 (1 H, br d, *J* 11.7, 6- or 2-H), 3.95–3.87 (1 H, m, 5-H), 3.80 (1 H, dd, $J_{2',3'}$ 9.0, $J_{3',4'}$ 9.7, 3-H), 3.71–3.66 (1 H, m, OH), 3.68 (1 H, dd, $J_{1',2'}$ 5.0, $J_{2',3'}$ 9.0, 2-H), 3.60 (1 H, d, J_{gem} 10.6, 6′-H), 3.50 (1 H, br d, *J* 11.7, OH), 3.45 (1 H, dd, $J_{5',6'}$ 7.0, J_{gem} 10.6, 6′-H), 3.27 (1 H, dd, $J_{3',4'}$ 9.7, $J_{4',5'}$ 9.2, 4′-H) and 1.99–1.35 (6 H, m, 3-, 4- and 5-H_2).

N-(2-*Aminoethyl*)-N′-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*thiourea* **37**.—To a solution of 1,2-diaminoethane (20 mm^3, 0.29 mmol) in CH_2Cl_2–MeOH (2.5 cm^3; 4:1, v/v) was added a solution of the isothiocyanate **31** (86 mg, 0.15 mmol) in CH_2Cl_2 (1.5 cm^3) dropwise at room temperature, and the mixture was stirred for 1.5 h. Evaporation of the mixture gave a syrupy residue, which was purified by a column of silica gel (3 g) with EtOH–toluene (1:5, v/v; 1% Et_3N) as eluent to give the *thiourea* **37** (76 mg, 80%) as a syrup (Found: C, 68.3; H, 6.8; N, 6.7. $C_{37}H_{43}N_2O_5S\cdot 1/2H_2O$ requires C, 68.3; H, 6.8; N, 6.5%); $[\alpha]_D^{21}$ +106 (*c* 2.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3330 (NH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.47 (1 H, br s, NH), 7.35–7.13 (20 H, m, 4 × Ph), 6.57 (1 H, br s, N′H), 5.10 (1 H, br d, $J_{1',2'}$ 4.8, 1′-H), 4.89 and 4.77 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.81 and 4.48 (each 1 H, ABq, J_{gem} 10.3, PhCH_2), 4.68 and 4.63 (each 1 H, ABq, J_{gem} 12.1, PhCH_2), 4.48 and 4.41 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 3.88 (1 H, ddd, $J_{4',5'}$ 9.3, $J_{5',6'}$ 1.5 and 4.5, 5′-H), 3.79 (1 H, dd, $J_{2',3'}$ 9.5, $J_{3,4}$ 8.8, 3-H), 3.67 (1 H, dd, $J_{1',2'}$ 4.8, $J_{2',3'}$ 9.5, 2′-H), 3.64 (1 H, dd, $J_{5',6'}$ 1.5, J_{gem} 10.6, 6′-H), 3.56–3.44 (4 H, m, 4- and 6′-H, and 1-H_2), 2.80–2.65 (2 H, m, 2-H_2) and 1.25 (br s, 2 H, NH_2).

2-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-1-*oxa*-3-*azacyclopentane* **38**.—To a stirred solution of the thiourea **32** (46 mg, 0.071 mmol) in diethyl ether (2 cm^3) were added three portions of yellow HgO (46 mg, 0.21 mmol), one every 3 h at room temperature, and the mixture was stirred for a further 17 h at room temperature. The reaction mixture was filtered through a bed of Celite and the filtrate was evaporated to give the *isourea*

38 (43 mg, 100%) as a syrup (Found: C, 72.7; H, 6.6; N, 4.5. $C_{37}H_{40}N_2O_6$ requires C, 73.0; H, 6.6; N, 4.6%); $[\alpha]_D^{25}$ +53.5 (*c* 1.16, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1680 (C=N); δ_H(270 MHz; $CDCl_3$) 7.35–7.10 (20 H, m, 4 × Ph), 5.49 (1 H, d, $J_{1,2}$ 5.1, 1-H), 4.91 and 4.77 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.79 and 4.51 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.66 and 4.61 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.61 and 4.46 (each 1 H, ABq, J_{gem} 12.1, PhCH_2), 4.29–4.23 (2 H, m) and 3.81–3.65 (8 H, m).

N-*Methyl*-2-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-1-*oxa*-3-*azacyclopentane* **39**.—The thiourea **33** (53 mg, 0.081 mmol) was similarly treated with yellow HgO (53 mg, 0.24 mmol × 3) for 19 h at room temperature to give the *isourea* **39** (47 mg, 94%) as a syrup (Found: C, 73.0; H, 7.0; N, 4.5. $C_{38}H_{42}N_2O_6$ requires C, 73.3; H, 6.8; N, 4.5%); $[\alpha]_D^{21}$ +83.4 (*c* 1.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1700 (C=N); δ_H(270 MHz; $CDCl_3$) 7.36–7.12 (20 H, m, 4 × Ph), 5.59 (1 H, d, $J_{1',2'}$ 4.0, 1-H), 4.96 and 4.79 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.84 and 4.49 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.75 and 4.64 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.63 and 4.49 (each 1 H, ABq, J_{gem} 12.5, PhCH_2), 4.37 (1 H, br dd, $J_{4',5'}$ 9.9, $J_{5',6'}$ 3.3, 5'-H), 4.25–4.04 (3 H, m), 3.77 (1 H, dd, $J_{5',6'}$ 3.3, J_{gem} 10.6, 6'-H), 3.72–3.62 (3 H, m), 3.43–3.28 (2 H, m) 2.83 (s, 3 H, NMe).

2-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-1-*oxa*-3-*azacyclohexane* **40**.—The thiourea **34** (68 mg, 0.10 mmol) was similarly treated with three portions of yellow HgO (67 mg, 0.31 mmol) in diethyl ether (2 cm^3) for 55 h at room temperature. After the usual work-up, the product was chromatographed on a column of silica gel (3 g) with EtOH–toluene (1:6, v/v) as eluent to afford the *isourea* **40** (42 mg, 66%) as a syrup (Found: C, 73.3; H, 6.9; N, 4.3%); $[\alpha]_D^{23}$ +60.7 (*c* 1.84, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (NH) and 1700 (C=N); δ_H(270 MHz; $CDCl_3$) 7.38–7.11 (20 H, m, 4 × Ph), 5.49 (1 H, d, $J_{1',2'}$ 4.4, 1'-H), 4.91 and 4.76 (each 1 H, ABq, J_{gem} 11.2, PhCH_2), 4.79 and 4.50 (each 1 H, ABq, J_{gem} 11.5, PhCH_2), 4.64 and 4.60 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.60 and 4.46 (each 1 H, ABq, J_{gem} 12.1, PhCH_2), 4.17 (2 H, dd, *J* 5.5 and 5.1), 3.84–3.63 (6 H, m), 3.44–3.26 (2 H, m) 1.91–1.78 (2 H, m, 2-H_2).

N-(4-*Hydroxybutyl*)-N'-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*carbodiimide* **41**.—The thiourea **35** (59 mg, 0.088 mmol) was treated with three portions of yellow HgO (57 mg, 0.26 mmol) in diethyl ether (2 cm^3) for 25 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was evaporated to give the *carbodiimide* **41** (54 mg, 96%) as a syrup (Found: C, 73.3; H, 6.8; N, 4.3. $C_{39}H_{44}N_2O_6$ requires C, 73.6; H, 7.0; N, 4.4%); $[\alpha]_D^{21}$ +65.1 (*c* 1.17, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH) and 2130 (N=C=N); δ_H(270 MHz; $CDCl_3$) 7.32–7.10 (20 H, m, 4 × Ph), 5.36 (1 H, d, $J_{1,2}$ 4.4, 1-H), 4.94 and 4.82 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.81 and 4.49 (each 1 H, ABq, J_{gem} 11.2, PhCH_2), 4.74 and 4.68 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.59 and 4.46 (each 1 H, ABq, J_{gem} 12.3, PhCH_2), 3.97 (1 H, br d, $J_{4',5'}$ 10.3, 5'-H), 3.89 (1 H, dd, $J_{2',3'}$ 9.2, $J_{3',4'}$ 9.2, 3'-H), 3.72 (1 H, dd, $J_{5',6'}$ 2.6, J_{gem} 9.9, 6-H), 3.68 (1 H, dd, $J_{1',2'}$ 4.4, $J_{2',3'}$ 9.2, 2'-H), 3.64–3.57 (4 H, m), 3.55–3.06 (2 H, m) and 1.62–1.50 (4 H, m, 2- and 3-H_2).

Mixture of (1R,2R,6S)- **42a** *and* (1S,2S,6R)-8-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-2-*hydroxy*-7-*oxa*-9-*azabicyclo*[4.3.0]*nonane* **42b**.—The thiourea **36** (102 mg, 0.14 mmol) was similarly treated with three portions of yellow HgO (93 mg, 0.43 mmol) in diethyl ether (2 cm^3) for 26 h at room temperature, to give, after the usual work-up, a *mixture of the isoureas* **42a, b** (88 mg, 91%) as a syrup (Found: C, 72.2; H, 6.9; N, 4.0. $C_{41}H_{46}N_2O_7$ requires C, 72.5; H, 6.8; N, 4.1%); ν_{max}(neat)/cm^{-1} 3250 (NH and OH) and 1660 (C=N); δ_H(270 MHz; $CDCl_3$) 7.38–7.08 (2 × 20 H, m 2 × 4 × Ph), 5.53 and 5.46 (each 1 H, 2 br s, 2 × 1'-H), 4.94–4.42 (2 × 10 H, m), 4.08–3.57 (2 × 8 H, m) and 1.95–1.20 (2 × 6 H, m).

2-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-1,3-*diazacyclopentane* **43**.—The thiourea **37** (48 mg, 0.074 mmol) was similarly treated with three portions of yellow HgO (48 mg, 0.22 mmol) for 19 h at room temperature to give the *guanidine* **43** (40 mg, 89%) as a syrup (Found: C, 72.3; H, 6.6; N, 6.7. $C_{37}H_{41}N_3O_5 \cdot 1/2H_2O$ requires C, 72.1; H, 6.9; N, 6.8%): $[\alpha]_D^{22}$ +94 (*c* 2.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3380 (NH) and 1650 (C=N); δ_H(270 MHz; $CDCl_3$) 7.34–7.13 (20 H, m, 4 × Ph), 5.13 (1 H, d, $J_{1,2}$ 4.0, 1-H), 5.00 and 4.79 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.83 and 4.46 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.73 and 4.67 (each 1 H, ABq, J_{gem} 12.8, PhCH_2), 4.50 and 4.41 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.06 (1 H, dd, $J_{2',3'}$ 8.8, $J_{3',4'}$ 8.8, 3'-H), 3.90 (1 H, ddd, $J_{4',5'}$ 9.9, $J_{5',6'}$ 2.9 and 7.2, 5'-H), 3.64 (1 H, dd, $J_{5',6'}$ 2.9, J_{gem} 9.7, 6'-H), 3.61 (1 H, dd, $J_{1',2'}$ 4.0, $J_{2',3'}$ 8.8, 2'-H), 3.51 (1 H, dd, $J_{5',6'}$ 7.2, J_{gem} 9.7, 6'-H), 3.42 (1 H, dd, $J_{3',4'}$ 8.8, $J_{4',5'}$ 9.9, 4'-H) and 3.29 (4 H, br s, NCH_2CH_2N).

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1R)-(1,2/3,4,5)-2,3,4,5-*tetrahydroxy*-5-(*hydroxymethyl*)*cyclopentyl*]-*thiourea* D-**44**.—A mixture of the isothiocyanate **39** (196 mg, 0.34 mmol) and the amino alcohol D-**24** (52 mg, 0.21 mmol) in aq. 75% DMF (8 cm^3) was stirred for 4 h at room temperature, and was then evaporated. The residual product was chromatographed on a column of silica gel (8 g) with EtOH–toluene (1:6, v/v) as eluent to give the *thiourea* D-**44** (201 mg, 91%) as a syrup (Found: C, 65.0; H, 6.4; N, 3.7%); $[\alpha]_D^{20}$ +138 (*c* 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3320 (OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.32–7.07 (20 H, m, 4 × Ph), 6.74 (1 H, s, NH), 5.74 (1 H, br s, N'H or OH), 5.00 (1 H, br d, $J_{1,2}$ 4.8, 1-H), 4.91 (1 H, br s, 1'-H), 4.93 and 4.78 (each 1 H, ABq, J_{gem} 10.8, PhCH_2), 4.81 and 4.42 (each 1 H, ABq, J_{gem} 10.8, PhCH_2), 4.69 and 4.60 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.45 and 4.40 (each 1 H, ABq, J_{gem} 12.7, PhCH_2), 4.15 and 3.99 (1 and 2 H, 2 d, *J* 4.8 and *J* 4.4, 2'-, 3'- and 4'-H), 3.83 (1 H, br dd, $J_{4,5}$ 9.9, $J_{5,6}$ 6.8, 5-H), 3.77 (1 H, dd, $J_{2,3}$ 9.2, $J_{3,4}$ 9.3, 3-H), 3.67 (1 H, dd, $J_{1,2}$ 4.8, $J_{2,3}$ 9.2, 2-H), 3.58 and 3.43 (each 1 H, ABq, J_{gem} 10.6, 6'-H) and 3.45–3.14 (3 H, m, 4-H and 6-H_2).

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1S)-(1,2/3,4,5)-2,3,4,5-*tetrahydroxy*-5-(*hydroxymethyl*)*cyclopentyl*]-*thiourea* L-**44**.—A mixture of the isothiocyanate **31** (197 mg, 0.34 mmol) and the amino alcohol L-**24** (54 mg, 0.30 mmol) in aq. 75% DMF (8 cm^3) was stirred for 3 h at room temperature. The product was chromatographed on a column of silica gel (8 g) with EtOH–toluene (1:6, v/v) as eluent to give the *thiourea* L-**44** (197 mg, 86%) as a syrup (Found: C, 65.0; H, 6.0; N, 3.3. $C_{41}H_{48}N_2O_{10}S$ requires C, 64.7; H, 6.4; N, 3.7%); $[\alpha]_D^{21}$ +59 (*c* 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3320 (OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.68 (1 H, d, $J_{1',N'H}$ 6.2, N'H), 7.37–7.12 (20 H, m, 4 × Ph), 6.65 (1 H, br s, NH), 4.93 (1 H, br s, OH), 4.91 (1 H, br s, 1-H), 4.91 and 4.79 (each 1 H, ABq, J_{gem} 10.8, PhCH_2), 4.81 and 4.55 (each 1 H, ABq, J_{gem} 11.5, PhCH_2), 4.77 and 4.46 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.69 (1 H, dd, $J_{1',5'}$ 6.2, H-1'), 4.43 and 4.37 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 3.89–3.30 (13 H, m, 2-, 3-, 5-, 2'-, 3'- and 4'-H, 6- and 6'-H_2, and 3 × OH), 3.24 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.2, 4-H) and 2.79 (1 H, br s, OH).

2,3,4,6-*Tetra*-O-*benzyl*-4'-*epitrehazolin* D-**45**.—To a stirred solution of the thiourea D-**44** (128 mg, 0.17 mmol) in acetone–diethyl ether (3.5 cm^3; 1:6, v/v) were added three portions of yellow HgO (109 mg, 0.50 mmol), one every 3 h at room temperature. The mixture was stirred further for 23 h and was then filtered through a bed of Celite, which was then thoroughly

washed with EtOH (50 cm^3). The combined filtrate and washings were evaporated to give the *isourea* D-**45** (125 mg, 100%) as a syrup (Found: C, 68.0; H, 6.4; N, 3.7. $C_{41}H_{46}N_2O_{10}$ requires C, 67.8; H, 6.4; N, 3.9%); $[\alpha]_D^{24}$ +38 (*c* 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (OH) and 1665 (NH); δ_H(270 MHz; $CDCl_3$) 7.30–7.08 (20 H, m, 4 × Ph), 5.33 (1 H, br s, 1-H), 4.89 and 4.77 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.83 (1 H, d, $J_{1',2'}$ 8.1, 2'-H), 4.76 and 4.54 (each 1 H, ABq, J_{gem} 11.3, PhCH_2), 4.62 and 4.58 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.44 and 4.40 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.41 (1 H, d, $J_{1',2'}$ 8.1, 1'-H), 4.01 (1 H, d, $J_{3',4'}$ 3.6, 3'- or 4'-H) and 4.01–3.56 (13 H, m, 2-, 3-, 4-, 5- and 4'- or 3'-H, 6- and 6'-H_2, and 4 × OH).

2,3,4,6-*Tetra*-O-*benzyl*-4'-*epitrehazolin Diastereoisomer* L-**45**.—The thiourea L-**44** (82 mg, 0.11 mmol) was similarly treated with three portions of yellow HgO (70 mg, 0.32 mmol) to give the *isourea* L-**45** (80 mg, 100%) as a syrup (Found: C, 67.6; H, 6.3; N, 3.8%); $[\alpha]_D^{23}$ +67 (*c* 0.95, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (OH) and 1670 (NH); δ_H(270 MHz; $CDCl_3$) 7.35–7.04 (20 H, m, 4 × Ph), 5.32 (1 H, br s, 1-H), 4.88 and 4.76 (each 1 H, ABq, J_{gem} 10.8, PhCH_2), 4.85 (1 H, d, $J_{1',2'}$ 7.9, 2'-H), 4.75 and 4.45 (each 1 H, ABq, J_{gem} 12.1, PhCH_2), 4.61 and 4.57 (each 1 H, ABq, J_{gem} 11.9, PhCH_2), 4.57 and 4.40 (each 1 H, ABq, J_{gem} 11.9, PhCH_2), 4.41 (1 H, d, $J_{1',2'}$ 7.9, 1'-H), 4.04 (1 H, d, $J_{3',4'}$ 4.8, 3'- or 4'-H), 3.81 (1 H, d, $J_{3',4'}$ 4.8, 4'- or 3'-H) and 3.79–3.58 (8 H, m, 2-, 3-, 4- and 5-H, and 6-and 6'-H_2).

Octa-N,O-*acetyl*-4'-*epitrehazolin* D-**46**.—To a mixture prepared from sodium (142 mg, 6.19 mmol) in liquid ammonia (5 cm^3) was added a solution of the isourea D-**45** (45 mg, 0.062 mmol) in THF (2 cm^3) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, and was then quenched by addition of excess of NH_4Cl (662 mg, 12.4 mmol). Ammonia spontaneously evaporated off and the residue was acetylated conventionally with acetic anhydride in pyridine. The mixture was evaporated, the residue was diluted with water (20 cm^3) and the solution was extracted with $CHCl_3$ (30 cm^3 × 3). The extracts were concentrated and the residual product was chromatographed on a column of silica gel (4 g) with acetone–toluene (1:3, v/v) as eluent to give the *octa*-N,O-*acetyl derivative* D-**46** (30 mg, 69%) as a syrup (Found: C, 49.2; H, 5.4; N, 3.8. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.5; N, 4.0%); $[\alpha]_D^{26}$ +93 (*c* 1.14, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480 (OH), 1745 (OAc) and 1695 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

Octa-N,O-*acetyl*-4'-*epitrehazolin Diastereoisomer* L-**46**.—The tetrakis-benzyl ether L-**45** (56 mg, 0.077 mmol) was similarly de-*O*-benzylated with a mixture prepared from sodium (177 mg, 7.70 mmol) in liquid ammonia (5 cm^3) to give, after acetylation and chromatography, the *octa*-N,O-*acetyl derivative* L-**46** (42 mg, 77%) as a syrup (Found: C, 49.6; H, 5.3; N. 4.4%); $[\alpha]_D^{25}$ +27 (*c* 1.67, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3480 (OH), 1745, 1735, 1730, 1715 (OAc) and 1695 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

(1S,5R,6R,7R,8S)-3-(α-D-*Glucopyranosylimino*)-6,7,8-*trihydroxy*-6-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* **1**.—(*a*) To liquid ammonia (~5 cm^3) containing sodium (150 mg, 6.6 mmol) was added a solution of the isourea D-**45** (48 mg, 0.066 mmol) in THF (1.5 cm^3) at −78 °C and the mixture was stirred for 10 min at the same temperature. After addition of NH_4Cl (530 mg, 9.9 mmol), ammonia evaporated off spontaneously. The residue was dissolved in water (10 cm^3) and the solution was washed with $CHCl_3$ (5 cm^3 × 2). The aqueous layer was taken up on a column of Dowex 50W X2 (H^+) resin (30 cm^3), which was eluted with 0.5 mol dm^{-3} NH_3 to give compound **1** (23 mg, 89%) as a powder, $[\alpha]_D^{22}$ +92 (*c* 0.61, water); ν_{max}(KBr disk)/cm^{-1} 3430 (OH) and 1660 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

Acetylation of compound **1** (20 mg, 0.051 mmol) with acetic anhydride (1 cm^3) and pyridine (0.5 cm^3) at room temperature gave, after chromatography, the octa-*N*,*O*-acetyl compound D-**46** (31 mg, 86%), identical with a sample obtained before.

(*b*) To a solution of the octa-*N*,*O*-acetyl compound D-**46** (21 mg, 0.031 mmol) in MeOH (1 cm^3) was added 1 mol dm^{-3} methanolic NaOMe (0.2 cm^3), and the mixture was stirred for 15 min at 0 °C. The product was purified as described above to give compound **1** (12 mg, 100%).

(1R,5S,6S,7S,8R)-3-(α-D-*Glucopyranosylimino*)-6,7,8-*trihydroxy*-6-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* **3**.—(*a*) The isourea L-**45** (52 mg, 0.072 mmol) was de-*O*-benzylated with a mixture prepared from sodium in liquid ammonia and the product was purified as in the preparation of compound **1** to give compound **3** (25 mg, 90%) as a powder, $[\alpha]_D^{22}$ +117 (*c* 0.77, water); ν_{max}(KBr disk)/cm^{-1} 3420 (OH) and 1650 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

Conventional acetylation of compound **3** (17 mg, 0.044 mmol) gave the octa-*N*,*O*-acetyl derivative L-**46** (26 mg, 85%).

(*b*) Similar treatment of the octa-*N*,*O*-acetyl compound L-**46** (31 mg, 0.044 mmol) with NaOMe in MeOH gave the free base **3** (16 mg, 90%) as a powder.

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1R)-(1,2,4/3,5)-2,3,4,5-*tetrahydroxy*-5-C-(*hydroxymethyl*)*cyclopentyl*]*thiourea* D-**47**.—A mixture of the isothiocyanate **31** (145 mg, 0.25 mmol) and the amino alcohol D-**30** (37 mg, 0.21 mmol) in aq. 75% DMF (4 cm^3) was stirred for 4 h at room temperature, and was then evaporated. The syrupy residue was chromatographed on a column of silica gel (15 g) with EtOH–toluene (1:12, v/v) as eluent to give the *thiourea* D-**47** (146 mg, 92%) as a syrup (Found: C, 64.5; H, 6.4; N, 3.7. $C_{41}H_{48}N_2O_{10}S$ requires C, 64.7; H, 6.4; N, 3.7%); $[\alpha]_D^{28}$ +134 (*c* 1.73, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3300 and 3250 (OH and NH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.63 (1 H, d, *J* 7.0, NH), 7.38–7.08 (20 H, m, 4 × Ph), 6.78 (1 H, br s, NH), 5.54 (1 H, s), 5.19 (1 H, br s), 4.91–4.38 (9 H, m) and 4.15–3.38 (15 H, m).

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1S)-(1,2,4/3,5)-2,3,4,5-*tetrahydroxy*-5-(*hydroxymethyl*)*cyclopentyl*]-*thiourea* L-**47**.—The isothiocyanate **31** (195 mg, 0.33 mmol) was similarly coupled with the amino alcohol L-**30** (40 mg, 0.22 mmol) to give the *thiourea* L-**47** (154 mg, 91%) as a syrup (Found: C, 64.5; H, 6.3; N, 3.6%); $[\alpha]_D^{23}$ +66 (*c* 1.08, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3400 and 3300 (OH and NH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.84 (1 H, d, $J_{1',N'H}$ 5.9, N'H), 7.35–7.06 (20 H, m, 4 × Ph), 6.72 (1 H, br s, NH), 5.20 (1 H, br s, 1-H), 4.87 and 4.74 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.76 and 4.42 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.69–4.64 (1 H, m, 1'-H), 4.66 and 4.57 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.47 and 4.38 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.06–3.51 (15 H, m) and 3.40 (1 H, dd, *J* 8.8 and 9.5, 4-H).

2,3,4,6-*Tetra*-O-*benzyltrehazolin* D-**48**.—To a mixture of the thiourea D-**47** (104 mg, 0.14 mmol) in diethyl ether (3 cm^3) were added three portions of yellow HgO (89 mg, 0.41 mmol), one every 3 h. The mixture was processed as in the preparation of compound D-**45** to give the *isourea* D-**48** (99 mg, 100%) as a syrup (Found: C, 67.5; H, 6.5; N, 3.8. $C_{41}H_{46}N_2O_{10}$ requires C, 67.8; H, 6.4; N, 3.9%); $[\alpha]_D^{27}$ +63 (*c* 1.27, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (OH) and 1660 (C=N); δ_H(270 MHz; $CDCl_3$) 7.33–7.09 (20 H, m, 4 × Ph), 5.33 (1 H, d, $J_{1,2}$ 4.8, 1-H), 4.90 and 4.75 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.77 and 4.44 (each 1 H, ABq, J_{gem} 11.0 PhCH_2), 4.76 (1 H, m, 2'-H), 4.59 and

4.53 (each 1 H, ABq, J_{gem} 11.7, PhCH_2), 4.47 and 4.39 (each 1 H, ABq, J_{gem} 11.5, PhCH_2), 4.30 (1 H, d, $J_{1',2'}$ 7.7, 1'-H), 3.90–3.63 (11 H, m, 3-, 5-, 6-, 3'- and 4'-H, 6'-H_2 and 4 × OH), 3.68 (1 H, dd, $J_{1,2}$ 4.8, $J_{2,3}$ 9.9, 2-H), 3.54 (1 H, dd, $J_{5,6}$ 5.9, J_{gem} 10.5, 6-H) and 3.42 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.2, 4-H).

2,3,4,6-*Tetra*-O-*benzyltrehazolin Diastereoisomer* L-**48**.—Similar treatment of the thiourea L-**47** (127 mg, 0.17 mmol) with yellow HgO gave the isourea L-**48** (113 mg, 93%) as a syrup (Found: C, 67.4; H, 6.1; N, 3.9%); $[\alpha]_D^{23}$ +56.3 (*c* 2.14, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH) and 1670 (C=N); δ_H(270 MHz; $CDCl_3$) 7.30–7.05 (20 H, m, 4 × Ph), 5.41 (1 H, br s, 1-H), 4.88 and 4.75 (each 1 H, ABq, J_{gem} 10.6, PhCH_2), 4.79 (1 H, d, $J_{1',2'}$ 8.6, 2'-H), 4.75 and 4.44 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.60 and 4.54 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.56 and 4.39 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.35 (1 H, d, $J_{1',2'}$ 8.6, 1'-H) and 4.05–3.60 (14 H, m, 2-, 3-, 4-, 5-, 3'- and 4'-H, 6-and 6'-H_2 and 4 × OH).

Octa-N,O-*acetyltrehazolin* D-**49**.—The isourea D-**48** (47 mg, 0.065 mmol) was de-*O*-benzylated and successively acetylated as in the preparation of compound D-**46** to give, after chromatography, the *octa*-N,O-*acetyl derivative* D-**49** (35 mg, 77%) as a syrup (Found: C, 49.2; H, 5.3; N, 3.7. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.5; N, 4.0%); $[\alpha]_D^{25}$ +104 (*c* 1.68, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (OAc) and 1700 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

Octa-N,O-*acetyltrehazolin Diastereoisomer* L-**49**.—Similar de-*O*-benzylation of the isourea L-**48** (45 mg, 0.062 mmol) followed by conventional acetylation gave the octa-*N*,*O*-acetyl compound L-**49** (35 mg, 80%) as a syrup (Found: C, 49.4; H, 5.3; N, 3.8%); $[\alpha]_D^{25}$ +30.2 (*c* 1.62, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (OAc) and 1700 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

(1S,5R,6R,7S,8S)-3-(α-D-*Glucopyranosylimino*)-6,7,8-*trihydroxy*-6-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* (*Trehazolin*) **2**.—(*a*) The tetrakis-benzyl ether D-**48** (47 mg, 0.065 mmol) was reduced with a mixture prepared from sodium in liquid ammonia and the product was purified as in the preparation of compound **1** to give trehazolin **2** (22 mg, 94%) as a powder, $[\alpha]_D^{23}$ +105 (*c* 0.36, water); ν_{max}(KBr disk)/cm^{-1} 3430 (OH) and 1650 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

Acetylation of compound **2** (22 mg, 0.060 mmol) gave the octa-*N*,*O*-acetyl derivative D-**49** (36 mg, 86%).

(*b*) De-*N*,*O*-acetylation of the octa-*N*,*O*-acetyl compound D-**49** (23 mg, 0.033 mmol) with methanoiic NaOMe (0.2 cm^3), and the product similarly purified, gave trehazolin **2** (12 mg, 100%).

(1R,5S,6S,7R,8R)-3-(α-D-*Gluocopyranosylimino*)-6,7,8-*trihydroxy*-6-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* (*Trehazolin diastereoisomer*) **4**.—(*a*) The tetrakis-benzyl ether L-**48** (31 mg, 0.043 mmol) was reduced and the product was purified as in the preparation of compound **1** to give the diastereoisomer **4** (15 mg, 92%) as a powder, $[\alpha]_D^{25}$ +63 (*c* 0.40, water); ν_{max}(KBr disk)/cm^{-1} 3430 (OH) and 1660 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

(*b*) De-*N*,*O*-acetylation of the octa-*N*,*O*-acetyl compound L-**49** (20 mg, 0.028 mmol) with sodium methoxide, and the product purified as in the preparation of compound **1**, gave the diastereoisomer **4** (8 mg, 76%).

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1R)-(1,2,5/3,4)-2,3,4,5-*tetrahydroxy*-2-(*hydroxymethyl*)*cyclopentyl*]*thiourea* L-**50**.—A mixture of the amino alcohol L-**25** (38 mg, 0.21 mmol) and the isothiocyanate **31** (145 mg, 0.25 mmol) in aq. 75% DMF (8 cm^3) was stirred for 4 h at room temperature, and was then evaporated. The residue was chromatographed on a column of silica gel (8 g) with EtOH–toluene (1:7, v/v) as eluent to give the *thiourea* L-**50** (146 mg, 90%) as a syrup (Found: C, 64.4; H, 6.0; N, 3.5. $C_{41}H_{48}N_2O_{10}S$ requires C, 64.7; H, 6.4; N, 3.7%); $[\alpha]_D^{21}$ +151 (*c* 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3340 (OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.63 (1 H, d, $J_{1',N'H}$ 8.8, N'H), 7.39–7.03 (20 H, m, 4 × Ph), 6.83 (1 H, br s, NH), 5.30 (1 H, br s, 1-H), 4.97 (1 H, dd, $J_{1',N'H}$ 8.8, $J_{1',2'}$ 7.7, 1'-H), 4.90 and 4.76 (each 1 H, ABq, J_{gem} 11.0, PhCH_2), 4.76 and 4.39 (each 1 H, ABq, J_{gem} 11.2, PhCH_2), 4.66 and 4.62 (each 1 H, ABq, J_{gem} 11.4, PhCH_2), 4.47 and 4.42 (each 1 H, ABq, J_{gem} 12.5, PhCH_2), 4.47–4.37 (2 H, m, 2 × OH), 4.18–4.08 (3 H, m, 2'-, 3'- and 4'-H), 3.83–3.56 (8 H, m, 2-, 3- and 5-H, 6- and 6'-H_2 and OH), 3.40 (1 H, br dd, $J_{2,3}$ 9.8, $J_{3,4}$ 9.8, 3-H), 3.28 (1 H, br dd, $J_{4,5}$ 9.8, 4-H), 3.08 (1 H, br s, OH) and 1.86 (1 H, br s, OH).

N-(2,3,4,6-*Tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-N'-[(1S)-(1,2,5/3,4)-2,3,4,5-*tetrahydroxy*-2-(*hydroxymethyl*)*cyclopentyl*]*thiourea* D-**50**.—A mixture of the isothiocyanate **31** (204 mg, 0.35 mmol) and the amino alcohol D-**25** (54 mg, 0.30 mmol) in aq. 75% DMF (8 cm^3) was stirred for 1 h at room temperature. The product was similarly purified to give the *thiourea* D-**50** (201 mg, 87%) as a syrup (Found: C, 64.7; H, 6.2; N, 3.5%); $[\alpha]_D^{20}$ +69 (*c* 1.01, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3330 (OH) and 1540 (NH); δ_H(270 MHz; $CDCl_3$) 7.57 (1 H, d, $J_{1',N'H}$ 8.1, N'H), 7.37–7.10 (20 H, m, 4 × Ph), 6.99 (1 H, br s, NH), 4.98 (1 H, br s, 1-H), 4.92, 4.80, 4.79, 4.75, 4.57 and 4.44 (each 1 H, 6 d, J_{gem} 10.6, 11.4, 10.3, 12.1, 12.1 and 11.1, 3 × PhCH_2), 4.67 (1 H, dd, $J_{1',N'H}$ 8.1, $J_{1',2'}$ 7.0, 1'-H), 4.45 and 4.40 (each 1 H, ABq, J_{gem} 11.9, PhCH_2), 4.07–3.43 (13 H, m, 2-, 3-, 5-, 2'-, 3'- and 4'-H, 6- and 6'-H_2 and 3 × OH), 3.33 (1 H, dd, $J_{3,4}$ 9.3, $J_{4,5}$ 9.3, 4-H), 2.90 (1 H, br s, OH) and 2.81 (1 H br s, OH).

Mixture of (1S,5R,6S,7R,8S)-6,7,8-*Trihydroxy*-6-*hydroxymethyl* L-**51** *and* (1S,5S,6S,7R,8R)-6,7,8-*Trihydroxy*-1-*hydroxymethyl*-3-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* L-**52**.—To a solution of the thiourea L-**50** (104 mg, 0.14 mmol) in acetone–diethyl ether (3.5 cm^3; 1:6, v/v) were added three portions of yellow HgO (88 mg, 0.41 mmol), one every 3 h. The mixture was stirred for 23 h at room temperature and was then filtered through a bed of Celite. Evaporation of solvent gave a *mixture of the isoureas* L-**51** and -**52** (100 mg, 100%) as a syrup (Found: C, 67.8; H, 6.6; N, 3.6. $C_{41}H_{46}N_2O_{10}$ requires C, 67.8; H, 6.4; N, 3.9%); ν_{max}(neat)/cm^{-1} 3370 (OH), and 1665 and 1655 (NH).

Mixture of (1R,5S,6R,7S,8R)-6,7,8-*Trihydroxy*-6-*hydroxymethyl* D-**51** *and* (1R,5R,6R,7S,8S)-6,7,8-*Trihydroxy*-1-*hydroxymethyl*-3-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosylimino*)-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* D-**52**.—The thiourea D-**50** (150 mg, 0.20 mmol) was treated with three portion of yellow HgO (128 mg, 0.59 mmol) for 18 h at room temperature, to give a *mixture of the isoureas* D-**51** and -**52** (139 mg, 97%) as a syrup (Found: C, 67.8; H, 6.3; N, 3.7%); ν_{max}(neat)/cm^{-1} 3380 (OH), and 1670 and 1655 (NH).

(1S,5R,6S,7R,8R)-7,8-*Diacetoxy*-6-*acetoxymethyl*-4-*acetyl*-6-*hydroxy*-3-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosylimino*)-L-**53** *and* (1S,5R,6S,7R,8R)-6,7,8-*Triacetoxy*-1-*acetoxymethyl*-4-*acetyl*-3-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosylimino*)-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* L-**54**.—A mixture (69 mg, 0.095 mmol) of the isoureas L-**51** and L-**52** was treated with a mixture prepared from sodium (218 mg, 9.47 mmol) in liquid ammonia (5 cm^3) for 15 min at −78 °C. After conventional acetylation, the product was chromatographed on a column of silica gel (4 g)

with acetone–toluene (1:3, v/v) as eluent to give, first, the *nona*-N,O-*acetyl derivative* L-**54** (26 mg, 39%) as a syrup (Found: C, 49.8; H, 5.3; N, 3.6. $C_{31}H_{40}N_2O_{19}$ requires C, 50.0; H, 5.4; N, 3.8%); $[\alpha]_D^{24}$ +49.2 (*c* 1.06, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750, 1735 and 1720 (OAc) and 1700 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

The second fraction gave the *octa*-N,O-*acetyl derivative* L-**53** (33 mg, 47%) as a syrup (Found: C, 49.2; H, 5.3; N, 3.7. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.5; N, 4.0%); $[\alpha]_D^{20}$ +87 (*c* 1.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3470 (OH), 1750, 1725 and 1720 (OAc) and 1695 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

(1R,5S,6R,7S,8S)-7,8-*Diacetoxy*-6-*acetoxymethyl*-4-*acetyl*-6-*hydroxy*-3-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosylimino*)-D-**53** *and* (1R,5S,6R,7S,8S)-6,7,8-*Triacetoxy*-1-*acetoxymethyl*-4-*acetyl*-3-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosylimino*)-2-*oxa*-4-*azabicylo*[3.3.0]*octane* D-**54**.—A mixture (52 mg, 0.071 mmol) of the isoureas D-**51** and D-**52** was treated with a mixture prepared from sodium (164 mg, 7.11 mmol) in liquid ammonia (5 cm^3) for 10 min at −78 °C. After the usual work-up, the product was acetylated conventionally and purified on a column of silica gel (4 g) with MeCN–toluene (2:5, v/v) as eluent to afford, first, the *nona*-N,O-*acetyl compound* D-**54** (24 mg, 45%) as a syrup (Found: C, 50.2; H, 5.3; N, 3.6. $C_{31}H_{40}N_2O_{19}$ requires C, 50.0; H, 5.4; N, 3.8%); $[\alpha]_D^{24}$ +79.2 (*c* 1.16, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1760, 1750, 1730, 1715 and 1705 (OAc) and 1695 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

The second fraction gave the *octa*-N,O-*acetyl compound* D-**53** (12 mg, 24%) as a syrup (Found: C, 49.2; H, 5.3; N, 3.7. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.5; N, 4.0%); $[\alpha]_D^{18}$ +56 (*c* 0.59, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3410 (OH), 1750, 1740, 1735, 1715 and 1695 (OAc) and 1690 (NAc and C=N); ^{1}H NMR spectroscopic data are listed in Table 2.

(1R,5S,6R,7S,8S)- D-**56** *and* (1S,5R,6S,7R,8R)-3-(α-D-*Gluco-pyranosylimino*)-6,7,8-*trihydroxy*-6-*hydroxymethyl*-2-*oxa*-4-*azabicyclo*[3.3.0]*octane* L-**56**.—The nona-*N*,*O*-acetyl compound L-**54** (27 mg, 0.036 mmol) was converted, as in the preparation of compound **1**, into the free base L-**56** (13 mg, 100%) as a powder, $[\alpha]_D^{23}$ +118 (*c* 0.65, water); ν_{max}(KBr disk)/cm^{-1} 3490 (OH) and 1660 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

De-*N*,*O*-acetylation of the nona-*N*,*O*-acetyl compound D-**54** (30 mg, 0.040 mmol) with methanolic NaOMe gave the free base D-**56** (14 mg, 100%) as a powder, $[\alpha]_D^{22}$ +48 (*c* 0.69, water); ν_{max}(KBr disk)/cm^{-1} 3420 (OH) and 1660 (C=N); ^{1}H NMR spectroscopic data are listed in Table 1.

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