# Synthesis of trehazolin analogues containing modified sugar moieties

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In order to elucidate the biological roles of the sugar moiety of the trehalase inhibitor trehazolin **1**, the sugar portion was first replaced with hydrophobic aromatic functions, providing the *N*-phenyl **3** and *N*-benzyl derivatives **4** of trehazolin **1**. Then the six analogues with the sugar moiety being replaced with D-mannopyranose **5**, 3-deoxy-*ribo*-hexopyranose **6**, D-galactopyranose **7**, 6-deoxy-D-glucopyranose **8**, 5a-carba-α-D-glucopyranose **9** and 5a-carba-α-D-*xylo*-hex-5(5a)-enopyranose residues **10** were synthesized.

In the hope of improving the fungicidal activity of trehazolin **1**, we prepared two disaccharide analogues, **11** and **12**, containing maltose and cellobiose residues. A remarkable decrease in potency was observed in the analogues **5**–**8** and **10**, but not for 5a'-carbatrehazolin **9**, suggesting an essential role for the D-*gluco* configuration of the hexopyranose portion. The β-D-glucosyl analogue **12** showed an increase in antifungal activity against *Rhizoctonia solani*, as compared with that of trehazolin **1**. The analogues **3** and **4** were not trehalase inhibitors, but rather were moderate α-glucosidase inhibitors.

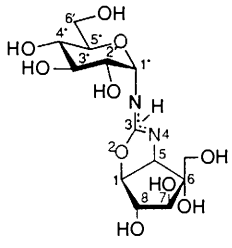
## Introduction

Trehazolin **1** was isolated in 1991 by Ando *et al.*[1] from the culture broth of *Micromonospora* strain SANK 62390, and was shown to exhibit very potent and specific inhibitory activity against trehalase *in vitro*. In connection with our synthetic studies[2] on glycoside hydrolase inhibitors, six trehazolin analogues containing modified aminocyclitol moieties were synthesized earlier[3] in order to elucidate the structure–activity relationships of this kind of inhibitor. It was shown that the stereochemistry of the hydroxy groups on the cyclopentane ring seemed to play an important role for exhibition of the activity; in particular, the *trans,trans*-1,2,3-triol structure as a mimic of α,α-trehalose was shown to be the essential core for potent trehalase inhibition.

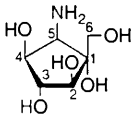
In this paper, we report a synthesis of eight trehazolin analogues **5**–**12** containing modified sugar moieties, together with the simple analogues **3** and **4** composed of an aromatic ring system, in order both to elucidate the role(s) of the glucopyranose residue and hopefully to increase its antifungal activity.

Antibiotic validamycins show potent fungicidal activity toward *Rhizoctonia solani*; however, when their β-D-glucopyranose residues are removed by hydrolysis, a derivative such as validoxylamine A, although a strong trehalase inhibitor *in vitro*, lacks antifungal activity,[4] due to its poor uptake into cells. Therefore, by analogy, it was expected that introduction of the D-glucopyranosyl residue at C-4' of trehazolin would improve its biological activity. Attempts were then made to synthesize the maltosyl **11** and cellobiosyl analogues **12**.

The synthesis involved coupling of the aminocyclitol trehazolamine[5] **2** and the appropriately protected sugar and carba-sugar isothiocyanates **16α**, **18α**, **20α**, **24α**, **27**, **29**, **31α** and **33α**, some of which were newly prepared, and subsequent cyclisation of the thiourea derivatives thus obtained by using yellow mercury(II) oxide[5] to afford the cyclic isoureas, followed by deprotection.



1 Trehazolin



2 Trehazolamine

## Results and discussion

### Synthesis of several glycosyl isothiocyanates

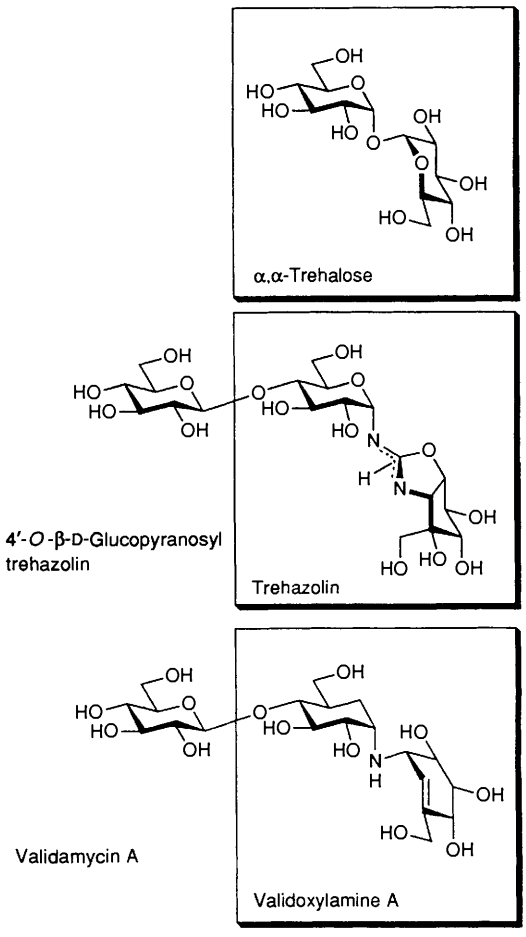
The synthesis was essentially according to the standard procedure, reported by Camarasa *et al.*[6] Thus, treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide **15** with an excess of KSCN in the presence of tetrabutylammonium bromide and molecular sieves in acetonitrile gave selectively, through neighbouring assistance of the 2-acetoxy group, the α-isothiocyanate[6] **16α**.

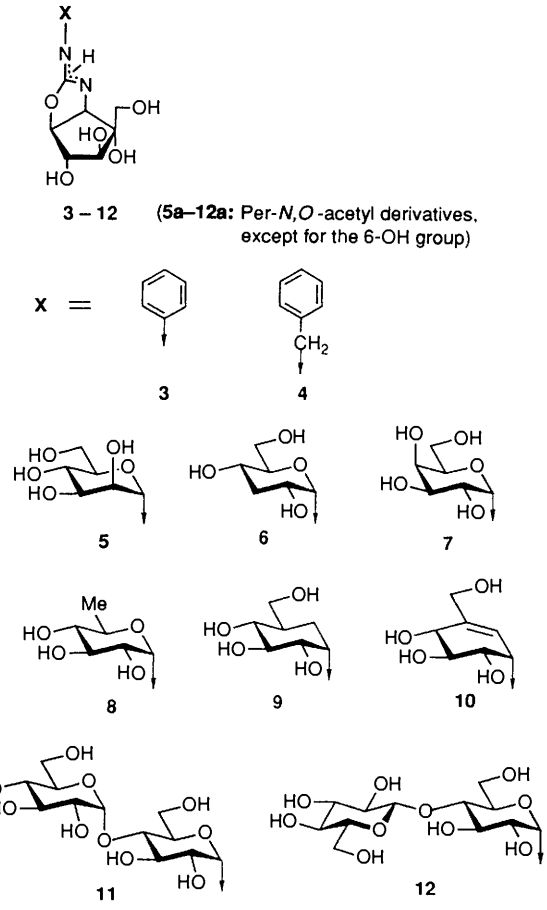
The sugar isothiocyanates other than the mannosyl were protected with benzyl ether groups, in order that only the hydroxy groups on the cyclopentane rings are able to attack the thiourea groups when treated with yellow HgO, thereby forming the cyclic isourea.

2,4,6-Tri-*O*-benzyl-3-deoxy-α- (**18α**) and -β-D-*ribo*-hexopyranosyl isothiocyanates (**18β**) were prepared from 2,4,6-tri-*O*-benzyl-3-deoxy-D-*ribo*-hexopyranose[7] **17** through a three-step sequence: acetylation (⟶ 1-acetate), treatment with hydrochloric acid (⟶ chloride), and then treatment with KSCN (⟶ isothiocyanates **18α,β**). The mixture was separated by a column of silica gel to give the α- **18α** (20% overall yield) and β-isothiocyanate **18β** (31%). In the $^1$H NMR spectra, the signals due to the α- and β-anomeric protons appeared as doublets at δ 5.50 (*J* 3.7 Hz) and 4.76 (*J* 8.4 Hz), respectively, supporting the structures assigned.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl chloride[8] **19** was similarly treated with an excess of KSCN to afford a 1:1 anomeric mixture of the isothiocyanates, which was separated by a column of silica gel, giving the syrupy α- **20α** (48%) and crystalline β-isothiocyanate **20β** (47%). The structure of compound **20α** was confirmed by IR and $^1$H NMR spectra, in which the signal of the anomeric proton appeared at δ 5.48 as a doublet (*J* 4.4 Hz).

2,3,4-Tri-*O*-benzyl-6-deoxy-α- (**24α**) and -β-D-glucopyranosyl isothiocyanates (**24β**) were prepared from methyl 6-deoxy-α-D-glucopyranoside[9] **21**. Thus, conventional benzylation of




compound **21** gave the 2,3,4-tris(benzyl ether) **22** (90%), which was hydrolysed and further acetylated to be converted into a mixture of the acetates **23α** (54%) and **23β** (44%). The mixture of acetates was directly chlorinated, and the single chloride formed selectively was treated with KSCN to give a mixture of the isothiocyanates, which was separated by chromatography to give compounds **24α** (24%) and **24β** (28%). Their $^1$H NMR spectra likewise supported the structures assigned.

2,3,4,6-Tetra-*O*-benzyl-5a-carba-α-D-glucopyranosyl isothiocyanate[10] **27** was prepared starting from the azide[11] **25**. Thus, after replacement of the protecting groups with the benzyl ether groups (⟶ **26**, 79%), the azido function was reduced with $LiAlH_4$ and the amine thus formed was converted into crystalline isothiocyanate **27** (67%) by treatment with 1,1′-thiocarbonyldiimidazole[12] in $CH_2Cl_2$.

4,7:5,6-Di-*O*-isopropylidenevalienamine†[13] **28** was similarly converted into the isothiocyanate derivative **29** in 96% yield.

2,2′,3,3′,4′,6,6′-Hepta-*O*-benzylmaltose[14] **30** was conventionally converted, after acetylation, into the isothiocyanates **31α** (24%) and **31β** (30%). 1-*O*-Acetyl-2,2′,3,3′,4′,6,6′-hepta-*O*-benzylcellobiose[15] **32α,β** was also converted into the corresponding isothiocyanates **33α** (21%) and **33β** (37%). The structures of the disaccharide isothiocyanates **31α** and **33α** were similarly established based on the $^1$H NMR signals due to the anomeric protons.

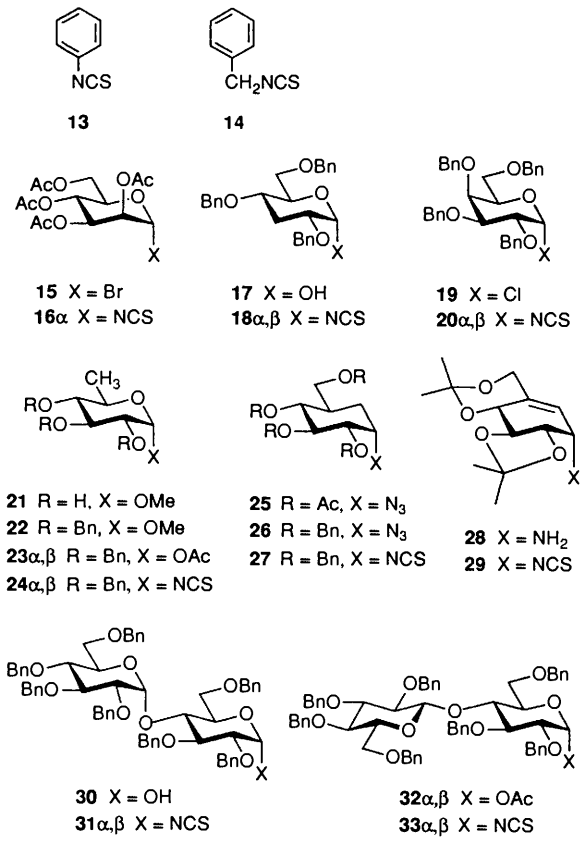
† We here propose naming the unsaturated carba-sugar, *i.e.* 'valienamine', 5a-carba-α-D-*xylo*-hex-5(5a)-enopyranosylamine, the unsaturation being located between C-5 and C-5a, in order to differentiate it from the *exo*-methylene derivative having unsaturation between C-5 and C-6.

**Synthesis of trehazolin analogues**

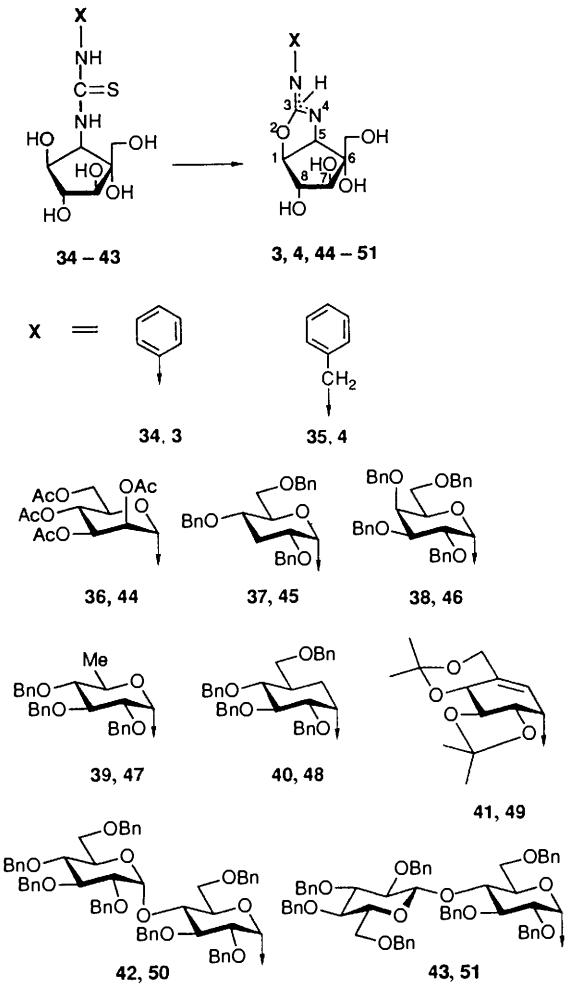
First, in order to explore the possibility of replacement of the sugar moiety with hydrophobic aryl functions as the spacer without affecting the activity, the *N*-phenyl- **3** and the *N*-benzyl-isourea derivatives **4** of trehazolamine **2** were synthesized by coupling of trehazolamine[5] **2** with phenyl **13** and benzyl isothiocyanates **14** (⟶ thioureas **34** and **35**), respectively, followed by successive cyclisation with excess of yellow HgO in acetone–EtOH (1 : 1) to afford the cyclic isoureas.

Then, the 2′-epimer **5** of trehazolin **1** was synthesized starting from the coupling product of trehazolamine **2** with the isothiocyanate **16α**. Thus, treatment of compound **2** and 1.4 molar equiv. of isothiocyanate **16α** in 75% aq. tetrahydrofuran (THF) at room temp. afforded the thiourea derivative **36** in 73% yield. On similar treatment (to that above) with HgO, compound **36** was readily converted into the cyclic isourea **44** quantitatively. Zemplén O-deacetylation of compound **44** afforded, after purification over a column of Dowex 50W-X2 ($H^+$) resin with aq. 0.5 mol $dm^{-3}$ ammonia as eluent, the free base **5** (72%), which was further characterised by conversion into the octa-*N*,*O*-acetyl derivative **5a** (82%) by treatment with acetic anhydride in pyridine. The structure of compound **5** was tentatively assigned on the basis of the IR and $^1$H NMR spectra of compounds **5** and **5a**. Their α-*manno* configuration was also deduced on the basis of the values of specific rotations, compared with those of α- and β-mannopyranosylamide derivatives.[16]

Next, the 3′-deoxy analogue **6** of compound **1** was synthesized from the coupling product **37** (91%) of trehazolamine **2** with isothiocyanate **18α**, followed by cyclisation (⟶ **45**, quantitatively) and O-debenzylation with sodium in liquid ammonia (⟶ **6**, quantitatively). The free base **6** was isolated pure on a column of similar acidic resin column with aq.




For convenience, only α-anomers of compounds **18**, **20**, **23**, **24**, **31** and **32** are depicted




0.125 mol dm$^{-3}$ ammonia, and characterised as the hepta-*N*,*O*-acetyl derivative **6a**. The structure **6** was fully established on the basis of the $^1$H NMR spectra of compounds **6** and **6a**. When the resin column was eluted with aq. 0.5 mol dm$^{-3}$ ammonia, compound **6** underwent partial isomerisation, giving ~1:1 mixture of compound **6** and the furanosylamine-type compound having a 2,6-dioxa-4-azabicyclo[3.3.0]octane ring structure.[1] In this case, the isomerisation was easily suppressed by using dil. aq. ammonia as eluent. Therefore, it may often be difficult to obtain isomerically pure free bases by deprotecting the per-*N*,*O*-acetyl derivatives.

The 4′-epimer **7** was similarly prepared from the coupling product **38** obtained from substrates **2** and **20a**, through cyclisation (⟶ **46**, quantitatively) and deprotection (⟶ **7**, 80%).

Likewise, the 6′-deoxy analogue **8** was prepared from the thiourea **39**, obtained from compounds **2** and **24α**, by a similar sequence of reactions: cyclisation (⟶ **47**, 98%) and deprotection (⟶ **8**, 78%).

The 5a-carbasugar analogue[10] **9** of trehazolin was synthesized by a similar sequence of reactions: coupling of substrates **2** and **27** to afford the thiourea **40** (62%), cyclisation to the cyclic isourea **48** (97%) and deprotection (⟶ **9**, quantitatively).

The valienamine analogue **10** was similarly synthesized by cyclisation of the thiourea **41** obtained from compounds **2** and **29**, followed by deprotection of the intermediate isourea **49**.

The structures of the free cyclic isoureas **7**–**10** were assigned by their conversion into the corresponding per-*N*,*O*-acetyl derivatives **7a**–**10a**, the structures of which were fully confirmed by their $^1$H NMR spectra.

The four analogues **5**–**8**, as well as trehazolin **1**, are isomerisable to the corresponding tautomers under prolonged storage, especially under basic conditions; however, the free bases **9** and **10** have been shown to be very stable.

Coupling of trehazolamine **2** with the disaccharide isothiocyanates **31a** and **33a** afforded the corresponding thioureas **42** and **43**, respectively, in good yield. Likewise, cyclisation of thioureas **42** and **43** with HgO afforded the cyclic isoureas **50** and **51**, which were easily deprotected to give the disaccharide analogues **11** and **12** in good yield, the structures of which were characterised as the respective per-*N*,*O*-acetyl derivatives **11a** and **12a**. It is of interest that these disaccharide analogues are comparatively stable under basic conditions.

In the per-*N*,*O*-acetyl derivatives **5a**–**12a** of the cyclic isoureas, the *N*-acetyl groups were deduced to be located at the ring nitrogen atoms,[3] by consideration of the $^1$H NMR spectra where the signals due to the anomeric protons 1′-H resonate at ~0.4 ppm downshifted as compared with those of the corresponding free bases, whereas the signals due to the protons 5-H attached to the isourea-ring nitrogen atoms shift to lower fields (~0.7 ppm), possibly largely influenced by the adjacent *N*-acetyl functions.

**Biological assay**

Ten trehazolin analogues **3**–**12** were, without further purification, subjected to biological assay on inhibitory activity against silkworm trehalase (Table 1). Two trehazolin analogues, **3** and **4**, having aromatic rings instead of sugar residues, did not show inhibitory activity at all. Two epimers, **5** and **7**, and two deoxy derivatives, **6** and **8**, all had decreased potency compared with trehazolin **1**. However, 5a′-carbatrehazolin **9** has been shown to be a potent inhibitor almost comparable to trehazolin

**Table 1** Inhibitory activity of ten trehazolin analogues against trehalase from silkworm[a]

| Compound | Inhibitory activity ($IC_{50}$/mol dm$^{-3}$) |
|---|---|
| Trehazolin **1** | $4.9 \times 10^{-8}$ (0.018)[b] |
| **3** | $> 5.0 \times 10^{-4}$ |
| **4** | $> 5.0 \times 10^{-4}$ |
| **5** | $3.7 \times 10^{-5}$ (14) |
| **6** | $1.2 \times 10^{-6}$ (0.43)[c] |
| **7** | $1.1 \times 10^{-4}$ (40) |
| **8** | $7.9 \times 10^{-6}$ (2.8) |
| **9** | $4.9 \times 10^{-8}$ (0.018) |
| **10** | $3.1 \times 10^{-7}$ (0.16) |
| **11** | $5.7 \times 10^{-6}$ (3) |
| **12** | $1.9 \times 10^{-7}$ (0.1) |

[a] Unless otherwise noted, trehazolin **1** as a reference compound showed $IC_{50}$ $4.88 \times 10^{-8}$ mol dm$^{-3}$ (0.018 μg cm$^{-3}$) against trehalase from silkworm. [b] Number in parentheses denotes $IC_{50}$ (μg cm$^{-3}$). [c] In this case, the reference compound **1** showed $IC_{50}$ (0.030 μg cm$^{-3}$).

**1**. These results suggested that the four hydroxy groups of the D-glucopyranosyl residue of trehazolin **1** were topologically essential for its binding to the active site of the enzyme through hydrogen bonding, and, substantially, the pseudo-disaccharide structures of compound **1** as well as compound **10** may be close mimics of the substrate α,α-trehalose or its intermediate which is involved in the substrate-recognition and/or hydrolytic step. The unsaturated analogue **10** containing a valienamine moiety therefore shows lower activity owing to conformation deformation of the 5a-carbahexopyranose ring. However, in the case of methyl α-acarviosin,[17] the 5a-carbaglycosylamine (valienamine) moiety is conversely thought to be a mimic of a flattened half-chair conformation of a glucosyl cation probably involved during hydrolysis of α-glucosides. Accordingly, the 3-amino-2-oxa-4-azabicyclo[3.3.0]octane (trehalamine)[18] moiety would constitute charge-distribution parts for binding the active site of the enzymes, and the simple cyclic isoureas **3** and **4** would then be expected to possess inhibitory activity against some glucosidases. In fact, compounds **3** and **4** have been demonstrated to be potent and specific α-glucosidase inhibitors [$IC_{50}$ $1.3 \times 10^{-6}$ and $4.8 \times 10^{-7}$ mol dm$^{-3}$ (yeast α-glucosidase) respectively],[19] and showed no observable activity against α- or β-galactosidase, β-glucosidase or α-mannosidase at a concentration less than $3.6 \times 10^{-4}$ mol dm$^{-3}$. The present results would open up possibilities for the preparation of effective glycosidase inhibitors[20] by using simple aminocyclopentanepolyol derivatives designed as mimics of intermediate glycosyl cations.[21]

The 4′-*O*-α-D-glucopyranosyl residue of the analogue **11** seems to hinder free interaction between its active core and the binding site of the enzyme, resulting in appreciable decrease of both *in vitro* and antifungal activity, compared with trehazolin **1**. However, 5a-carbatrehazolin **9** completely lacks antifungal activity. It is interesting to note that, although somewhat weaker in its *in vitro* activity, the cellobiosyl analogue **12**, as had been expected, was estimated to be more effective toward *Rhizoctonia solani* than was the parent trehazolin. The β-D-glucopyranosyl residue is likely to facilitate uptake of the inhibitor into the cell, similarly as shown in the related antibiotic validamycins.[4]

## Experimental

### General methods

Mps were determined with a MEL-TEMP capillary melting point apparatus and are uncorrected. Unless otherwise noted, $^1$H NMR spectra were recorded for solutions in $CDCl_3$ (internal $Me_4Si$) or $D_2O$ (internal acetone) with a JEOL EX-90 (90 MHz) or JEOL GSX-270 (270 MHz) instrument, and *J* values are given in Hz. IR spectra were recorded with a JASCO IR-810 or Hitachi FTS-65 spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter, and $[\alpha]_D$-values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. TLC was performed on Silica Gel 60 F254 (E. Merck, Darmstadt) with detection by charring with sulfuric acid. Column chromatography was conducted on Wakogel C-300 (Wako Junyaku Kogyo Co., Osaka, Japan; 300 mesh) or Silica Gel 60 K070 (Katayama Kagaku Kogyo Co., Osaka, Japan). Organic solutions were dried over anhydrous $Na_2SO_4$ and concentrated at < 45 °C under diminished pressure.

The free isoureas **5**–**12** obtained by deprotection of the corresponding protected derivatives **44**–**51** were directly subjected to biological assay, as well as to acetylation to the per-*N*,*O*-acetyl derivatives for characterisation.

Biological assay on the inhibitory activity against α-glucosidase (Bakers' yeast, EC 3.2.1.20) was carried out following the standard procedure:[19] *p*-nitrophenyl α-D-glucopyranoside (0.66 mmol dm$^{-3}$), phosphate buffer (100 mmol dm$^{-3}$), pH 6.8, 30 min (37 °C).

### 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl isothiocyanate 16α

According to the standard procedure,[5] the title isothiocyanate **16α** was prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide **15**; a syrup, $[\alpha]_D^{24}$ +144 (*c* 0.39, $CHCl_3$) {lit.,[4] mp 92–94 °C; $[\alpha]_D$ +132 (*c* 1, $CHCl_3$)}; $\delta_H$(90 MHz; $CDCl_3$) 5.56 (1 H, d, $J_{1,2}$ 2.0, 1-H), 5.37–5.26 (3 H, m, 2-, 3- and 4-H), 4.43–4.03 (3 H, m, 5-H and 6-$H_2$) and 2.19, 2.13, 2.08 and 2.03 (each 3 H, 4 s, 4 × Ac).

### 2,4,6-Tri-*O*-benzyl-3-deoxy-α- **18α** and -β-D-*ribo*-hexopyranosyl isothiocyanates **18β**

Conventional acetylation of 2,4,6-tri-*O*-benzyl-3-deoxy-D-*ribo*-hexopyranose[6] **17** (1.50 g, 3.45 mmol) with acetic anhydride and pyridine overnight at room temp. gave, after chromatography on silica gel [30 g (1:4) EtOAc–hexane], the acetate (1.61 g, 98.2%), which was treated with 1,4-dioxane (30 cm$^3$) saturated with HCl gas at room temp. for 2 h at 38 °C. Evaporation of the mixture afforded a crude glycosyl chloride.

To a suspension of KSCN (735 mg, 7.56 mmol, 3 mol equiv.), $Bu_4NBr$ (812 mg, 2.52 mmol, 1 mol equiv.), and molecular sieves 4 Å (800 mg) in acetonitrile (30 cm$^3$) was added a solution of the crude chloride in acetonitrile (30 cm$^3$), and the mixture was stirred for 2 h at reflux. After cooling, the reaction mixture was filtered through a bed of Celite, and the filtrate was washed with EtOAc and evaporated to give a syrupy residue. The product was chromatographed on a column of silica gel (43 g), with EtOAc–hexane (1:20, v/v) as eluent to give, first, the β-*isothiocyanate* **18β** (370 mg, 31.1%) as crystals; mp 65–66 °C (from hexane) (Found: C, 70.7; H, 6.45; N, 2.8. $C_{28}H_{29}NO_4S$ requires C, 70.7; H, 6.15; N, 2.95%); $[\alpha]_D^{24}$ +42.5 (*c* 1.25, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2010 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.16 (15 H, m, 3 × Ph), 4.76 (1 H, d, $J_{1,2}$ 8.4, 1-H), 4.70 and 4.63 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.61 and 4.53 (each 1 H, ABq, $J_{gem}$ 12.3, PhC$H_2$), 4.54 and 4.39 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 3.72 (1 H, dd, $J_{5,6a}$ 1.7, $J_{gem}$ 10.6, 6-H$^a$), 3.65 (1 H, dd, $J_{5,6b}$ 4.0, $J_{gem}$ 10.6, 6-H$^b$), 3.52 (1 H, ddd, $J_{3eq,4}$ 4.4, $J_{3ax,4}$ 10.3, $J_{4,5}$ 10.4, 4-H), 3.48 (1 H, ddd, $J_{5,6}$ 1.7 and 4.0, $J_{4,5}$ 10.4, 5-H), 3.41 (1 H, ddd, $J_{2,3eq}$ 4.8, $J_{2,3ax}$ 11.4, $J_{1,2}$ 8.4, 2-H), 2.59 (1 H, ddd, $J_{2,3eq}$ 4.8, $J_{3eq,4}$ 4.4, $J_{gem}$ 12.1, 3-H$^{eq}$) and 1.48 (1 H, ddd, $J_{2,3ax}$ 11.4, $J_{3ax,4}$ 10.3, $J_{gem}$ 12.1, 3-H$^{ax}$).

The second fractions gave the α-*isothiocyanate* **18α** (238 mg, 20.1%) as a syrup (Found: C, 70.6; H, 6.2; N, 2.9%); $[\alpha]_D^{25}$ +110 (*c* 1.22, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2010 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.38–7.20 (15 H, m, 3 × Ph), 5.50 (1 H, d, $J_{1,2}$ 3.7, 1-H), 4.60 (2 H, s, PhC$H_2$), 4.59 and 4.48 (each 1 H, ABq, $J_{gem}$

12.3, PhC$H_2$), 4.56 and 4.38 (each 1 H, ABq, each 1 H, $J_{gem}$ 11.4, PhC$H_2$), 3.77 (1 H, dd, $J_{5,6a}$ 3.3, $J_{gem}$ 8.4, 6-H$^a$), 3.73 (1 H, dd, $J_{5,6b}$ 3.7, $J_{gem}$ 8.4, 6-H$^b$), 3.67–3.60 (1 H, m, 5-H), 3.64 (1 H, ddd, $J_{1,2}$ 3.7, $J_{2,3eq}$ 4.0, $J_{2,3ax}$ 11.7, 2-H), 3.58–3.53 (1 H, m, 4-H), 2.43 (1 H, ddd, $J_{2,3eq}$ 4.0, $J_{3eq,4}$ 4.4, $J_{gem}$ 12.1, 3-H$^{eq}$) and 1.77 (1 H, ddd, $J_{2,3ax}$ 11.7, $J_{3ax,4}$ 11.0, $J_{gem}$ 12.1, 3-H$^{ax}$).

**2,3,4,6-Tetra-*O*-benzyl-α- 20α and β-D-galactopyranosyl isothiocyanate 20β**

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl chloride[7] **19** (1.23 g, 2.22 mmol) was treated with KSCN similarly as in the preparation of compounds **18α,β** to give, first, the *α-isothiocyanate* **20α** (613 mg, 47.9%) as a syrup (Found: C, 72.4; H, 6.1; N, 2.4. $C_{35}H_{35}NO_5S$ requires C, 72.3; H, 6.1; N, 2.4%); $[\alpha]_D^{25}$ +103 (*c* 1.65, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2010 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.39–7.21 (20 H, m, 4 × Ph), 5.48 (1 H, d, $J_{1,2}$ 4.4, 1-H), 4.92 and 4.54 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.83 and 4.73 (each 1 H, ABq, $J_{gem}$ 11.5, PhC$H_2$), 4.83 and 4.69 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.47 and 4.39 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.13 (1 H, dd, $J_{1,2}$ 4.4, $J_{2,3}$ 9.7, 2-H), 4.00–3.94 (2 H, m, 4-, 5-H), 3.78 (1 H, dd, $J_{2,3}$ 9.7, $J_{3,4}$ 2.7, 3-H), 3.51 (1 H, dd, $J_{5,6a}$ 6.0, $J_{gem}$ 9.3, 6-H$^a$) and 3.46 (1 H, dd, $J_{5,6b}$ 6.8, $J_{gem}$ 9.3, 6-H$^b$).

The second fractions gave the β-*isothiocyanate* **20β** (604 mg, 47.1%) as crystals; mp 98–99 °C (from hexane) (Found: C, 72.45; H, 6.1; N, 2.4%); $[\alpha]_D^{25}$ +5.1 (*c* 1.38, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2000 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.39–7.23 (20 H, m, 4 × Ph), 4.93 and 4.59 (each 1 H, ABq, $J_{gem}$ 11.5, PhC$H_2$), 4.88 (2 H, s, PhC$H_2$), 4.78 (1 H, d, $J_{1,2}$ 8.4, 1-H), 4.73 and 4.68 (each 1 H, ABq, $J_{gem}$ 11.9, PhC$H_2$), 4.47 and 4.40 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$) and 3.96–3.89 and 3.59–3.50 (2 and 4 H, 2 m, 2-, 3-, 4- and 5-H and 6-$H_2$).

**Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside 22**

Methyl 6-deoxy-α-D-glucopyranoside[8] **21** (1.73 g, 9.71 mmol) was treated with 60% NaH (3.50 g, 87.4 mmol, 9 mol equiv.) in dimethylformamide (DMF) (20 cm$^3$) for 30 min at 0 °C. To the mixture was then added BnBr (7.1 cm$^3$, 58.3 mmol, 6 mol equiv.) and it was stirred for 2 h at room temp. The reaction mixture was then diluted with EtOAc (300 cm$^3$), washed with water (150 cm$^3$ × 5) and dried. Removal of the solvent gave a syrupy residue, which was chromatographed on a column of silica gel (280 g) with EtOAc–hexane (1:12, v/v) to afford the *tris(benzyl ether)* **22** (3.90 g, 89.7%) as a syrup (Found: C, 74.6; H, 7.4. $C_{28}H_{32}O_5$ requires C, 75.0; H, 7.2%); $[\alpha]_D^{27}$ +17.0 (*c* 1.45, $CHCl_3$); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.22 (15 H, m, 3 × Ph), 4.97 and 4.81 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.89 and 4.62 (each 1 H, ABq, $J_{gem}$ 10.8, PhC$H_2$), 4.79 and 4.66 (each 1 H, ABq, $J_{gem}$ 12.1, PhC$H_2$), 4.52 (1 H, d, $J_{1,2}$ 3.7, 1-H), 3.95 (1 H, dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.2, 3-H), 3.72 (1 H, dq, $J_{4,5}$ 9.5, $J_{5,6}$ 6.6, 5-H), 3.51 (1 H, dd, $J_{1,2}$ 3.7, $J_{2,3}$ 9.9, 2-H), 3.36 (3 H, s, 3 H, OMe), 3.11 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.5, 4-H) and 1.23 (3 H, d, $J_{5,6}$ 6.6, Me).

**1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-6-deoxy-α- 23α and -β-D-glucopyranose 23β**

The methyl glucoside **22** (3.40 g, 7.58 mmol) was hydrolysed with 80% aq. 1,4-dioxane (40 cm$^3$) containing 5 mol dm$^{-3}$ $H_2SO_4$ (1 cm$^3$) for 7 days at 80 °C. After neutralisation with $NaHCO_3$, the mixture was evaporated, the residue was diluted with EtOAc (300 cm$^3$), and the solution was washed with water (150 cm$^3$ × 3) and dried. Evaporation of the mixture gave a syrupy residue, which was chromatographed on a column of silica gel (150 g) with EtOAc–hexane (1:5, v/v) as eluent to afford the tris(benzyl ether) (150 g, 45.6%) as crystals.

This compound (1.50 g, 3.45 mmol) was acetylated conventionally to give, first, after chromatography on silica gel (120 g) with EtOAc–hexane (1:3, v/v) as eluent, the β-*acetate* **23β** (723 mg, 44.1%) as crystals; mp 108–109 °C (from hexane) (Found: C, 72.8; H, 6.8. $C_{29}H_{32}O_6$ requires C, 73.1; H, 6.8%); $[\alpha]_D^{27}$ +16.3 (*c* 0.28, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 1750 (OAc); $\delta_H$(270 MHz; $CDCl_3$) 7.37–7.16 (15 H, m, 3 × Ph), 5.60 (1 H, d, $J_{1,2}$ 8.1, 1-H), 4.90 and 4.82 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.88 and 4.65 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.79 and 4.74 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 3.69 (1 H, dd, $J_{2,3}$ 9.2, $J_{3,4}$ 9.2, 3-H), 3.55 (1 H, dq, $J_{4,5}$ 9.2, $J_{5,6}$ 6.2, 5-H), 3.55 (1 H, dd, $J_{1,2}$ 8.1, $J_{2,3}$ 9.2, 2-H), 3.21 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.2, 4-H), 2.05 (3 H, s, Ac) and 1.30 (3 H, d, $J_{5,6}$ 6.2, Me).

The second fractions gave the *α-acetate* **23α** (877 mg, 53.5%) as crystals; mp 125–126 °C (from hexane) (Found: C, 72.7; H, 7.1%); $[\alpha]_D^{25}$ +47.9 (*c* 0.56, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 1745 (OAc); $\delta_H$(270 MHz; $CDCl_3$), 7.38–7.20 (15 H, m, 3 × Ph), 6.24 (1 H, d, $J_{1,2}$ 3.3, 1-H), 4.96 and 4.82 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.90 and 4.63 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.70 and 4.63 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 3.91 (1 H, dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.2, 3-H), 3.85 (1 H, dq, $J_{4,5}$ 9.5, $J_{5,6}$ 6.2, 5-H), 3.64 (1 H, dd, $J_{1,2}$ 3.3, $J_{2,3}$ 9.5, 2-H), 3.18 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.5, 4-H), 2.14 (3 H, s, Ac) and 1.26 (3 H, d, $J_{5,6}$ 6.2, Me).

**2,3,4-Tri-*O*-benzyl-6-deoxy-α- 24α and -β-D-glucopyranosyl isothiocyanate 24β**

A mixture of the α- and β-acetate **23α,β** (1.30 g, 2.73 mmol) was treated with 1,4-dioxane (30 cm$^3$; saturated with HCl) for 10 min at 38 °C. Evaporation of the mixture left a syrupy residue, which was converted as in the preparation of compound **18α,β** into a mixture of the isothiocyanates. Column chromatography (170 g) with EtOAc–hexane (1:25, v/v) as eluent afforded, first, the β-*isothiocyanate* **24β** (366 mg, 28.2%) as crystals; mp 114–115 °C (from hexane) (Found: C, 70.5; H, 6.2; N, 2.9. $C_{28}H_{29}NO_4S$ requires C, 70.7; H, 6.15; N, 2.95%); $[\alpha]_D^{24}$ −2.6 (*c* 1.60, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2000 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.38–7.23 (15 H, m, 3 × Ph), 4.91 and 4.83 (each 1 H, ABq, $J_{gem}$ 10.3, PhC$H_2$), 4.90 and 4.84 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.86 and 4.64 (each 1 H, ABq, $J_{gem}$ 10.7, PhC$H_2$), 4.78 (1 H, d, $J_{1,2}$ 8.4, 1-H), 3.61 (1 H, dd, $J_{2,3}$ 8.8, $J_{3,4}$ 8.8, 3-H), 3.50 (1 H, dd, $J_{1,2}$ 8.4, $J_{2,3}$ 8.8, 2-H), 3.43 (1 H, dq, $J_{4,5}$ 9.5, $J_{5,6}$ 6.2, 5-H), 3.21 (1 H, dd, $J_{3,4}$ 8.8, $J_{4,5}$ 9.5, 4-H) and 1.31 (3 H, d, $J_{5,6}$ 6.2, Me).

The second fractions gave the *α-isothiocyanate* **24α** (310 mg, 23.9%) as a syrup (Found: C, 70.4; H, 6.3; N, 2.9%); $[\alpha]_D^{24}$ +118 (*c* 1.50, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2035 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.38–7.20 (15 H, m, 3 × Ph), 5.34 (1 H, d, $J_{1,2}$ 4.0, 1-H), 4.94 and 4.82 (each 1 H, ABq, $J_{gem}$ 10.8, PhC$H_2$), 4.88 and 4.62 (each 1 H, ABq, $J_{gem}$ 10.6, PhC$H_2$), 4.76 and 4.68 (each 1 H, ABq, each 1 H, $J_{gem}$ 11.9, PhC$H_2$), 3.83 (1 H, dd, $J_{2,3}$ 9.2, $J_{3,4}$ 9.2, 3-H), 3.82 (1 H, dq, $J_{4,5}$ 9.5, $J_{5,6}$ 6.2, 5-H), 3.63 (1 H, dd, $J_{1,2}$ 4.0, $J_{2,3}$ 9.2, 2-H), 3.11 (1 H, dd, $J_{3,4}$ 9.2, $J_{4,5}$ 9.5, 4-H) and 1.24 (3 H, d, $J_{5,6}$ 6.2, Me).

**2,3,4,6-Tetra-*O*-benzyl-5a-carba-α-D-glucopyranosyl azide 26**

2,3,4,6-Tetra-*O*-acetyl-5a-carba-α-D-glucopyranosyl azide[10] **25** (414 mg, 1.11 mmol) was treated with 1 mol dm$^{-3}$ methanolic NaOMe (1 cm$^3$) in MeOH (9 cm$^3$) for 1.5 h at room temp. After neutralisation with Amberlite IR 120B ($H^+$) resin, the solution was evaporated to give a syrupy residue, which was treated with 60% NaH (357 mg, 8.91 mmol, 8 mol equiv.) in DMF (8 cm$^3$) for 30 min at 0 °C. Then BnBr (1.1 cm$^3$, 8.91 mmol, 8 mol equiv.) was added to the reaction mixture at 0 °C which was then stirred for 3 h at room temp. After addition of a small amount of MeOH, the mixture was diluted with EtOAc (80 cm$^3$), washed with water (50 cm$^3$ × 5), dried, and evaporated. The residue was chromatographed on a column of silica gel (30 g) with EtOAc–hexane (1:10, v/v) as eluent to give the *tetrakis(benzyl ether)* **26** (498 mg, 79.2%) as crystals, mp 106–107 °C (from EtOH) (Found: C, 74.85; H, 6.7; N, 7.1. $C_{35}H_{37}N_3O_4$ requires C, 74.6; H, 6.6; N, 7.45%); $[\alpha]_D^{25}$ +42.3 (*c* 1.31, $CHCl_3$);

$\nu_{max}$(neat)/cm$^{-1}$ 2100 ($N_3$); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.19 (20 H, m, 4 × Ph), 4.94 and 4.81 (each 1 H, ABq, $J_{gem}$ 10.8, PhC$H_2$), 4.88 and 4.50 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.73 (2 H, s, PhC$H_2$), 4.41 (2 H, s, PhC$H_2$), 3.99 (1 H, ddd, $J_{1,2}$ 3.5, $J_{1,5a}$ 3.7 and 2.9, 1-H), 3.87 (1 H, dd, $J_{2,3}$ 9.2, $J_{3,4}$ 9.5, 3-H), 3.67 (1 H, dd, $J_{5,6a}$ 3.5, $J_{gem}$ 9.2, 6-H$^a$), 3.54 (1 H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 9.2, 2-H), 3.45 (1 H, dd, $J_{3,4}$ 9.5, $J_{4,5}$ 11.0, 4-H), 3.39 (1 H, dd, $J_{5,6b}$ 2.6, $J_{gem}$ 9.2, 6-H$^b$), 1.98 (1 H, ddddd, $J_{4,5}$ 11.0, $J_{5,5a}$ 3.7 and 12.7, $J_{5,6}$ 3.5 and 2.6, 5-H), 1.82 (1 H, ddd, $J_{1,5a\text{-}eq}$ 3.7, $J_{5,5a\text{-}eq}$ 3.7, $J_{gem}$ 14.3, 5a-H$^{eq}$) and 1.57 (1 H, ddd, $J_{1,5a\text{-}ax}$ 2.9, $J_{5,5a\text{-}ax}$ 12.7, $J_{gem}$ 14.3, 5a-H$^{ax}$).

### 2,3,4,6-Tetra-*O*-benzyl-5a-carba-α-D-glucopyranosyl isothiocyanate 27

The azide **26** (498 mg, 0.883 mmol) was treated with $LiAlH_4$ (268 mg, 7.06 mmol, 8 mol equiv.) in diethyl ether (10 cm$^3$) for 2.5 h at room temp. After decomposition of excess of reagent by addition of water, the mixture was extracted with $CHCl_3$ (40 cm$^3$ × 3) and the organic layers were dried and evaporated to dryness. The residue was treated with 1,1′-thiocarbonyldiimidazole (472 mg, 2.65 mmol, 3 mol equiv.) in $CH_2Cl_2$ (9 cm$^3$) for 1.2 h at room temp. The mixture was evaporated and the residual product was chromatographed on a column of silica gel [30 g, EtOAc–hexane (1 : 20, v/v)] to give the *isothiocyanate* **27** (356 mg, 67.0%) as crystals; mp 103–104 °C (from hexane) (Found: C, 74.6; H, 6.5; N, 2.4. $C_{36}H_{37}NO_4S$ requires C, 74.6; H, 6.4; N, 2.4%); $[\alpha]_D^{27}$ +99.2 (*c* 0.79, $CHCl_3$); $\nu_{max}$(KBr disk)/cm$^{-1}$ 2080 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.39–7.19 (20 H, m, 4 × Ph), 4.95 and 4.81 (each 1 H, ABq, $J_{gem}$ 10.6, PhC$H_2$), 4.89 and 4.50 (each 1 H, ABq, $J_{gem}$ 10.6, PhC$H_2$), 4.73 and 4.67 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.41 (2 H, s, PhC$H_2$), 4.25 (1 H, ddd, $J_{1,2}$ 2.0, $J_{1,5a}$ 3.5 and 2.9, 1-H), 3.81 (1 H, dd, $J_{2,3}$ 9.2, $J_{3,4}$ 9.5, 3-H), 3.72 (1 H, dd, $J_{5,6a}$ 4.0, $J_{gem}$ 9.2, 6-H$^a$), 3.49 (1 H, dd, $J_{3,4}$ 9.5, $J_{4,5}$ 8.8, 4-H), 3.46 (1 H, dd, $J_{1,2}$ 2.0, $J_{2,3}$ 9.2, 2-H), 3.42 (1 H, dd, $J_{5,6b}$ 2.4, $J_{gem}$ 9.2, 6-H$^b$), 2.06 (1 H, ddddd, $J_{4,5}$ 8.8, $J_{5,5a}$ 3.5 and 12.6, $J_{5,6}$ 4.0 and 2.4, 5-H), 1.92 (1 H, ddd, $J_{1,5a\text{-}eq}$ 3.5, $J_{5,5a\text{-}eq}$ 3.5, $J_{gem}$ 14.7, 5a-H$^{eq}$) and 1.59 (1 H, ddd, $J_{1,5a\text{-}ax}$ 2.9, $J_{5,5a\text{-}ax}$ 12.6, $J_{gem}$ 14.7, 5a-H$^{ax}$).

### 2,3:4,6-Di-*O*-isopropylidene-5a-carba-α-D-*xylo*-hex-5(5a)-enopyranosyl isothiocyanate 29

To a solution of 4,7 : 5,6-di-*O*-isopropylidenevalienamine **28**[13] (138 mg, 0.541 mmol) in $CH_2Cl_2$ (6 cm$^3$) was added 1,1′-thiocarbonyldiimidazole (289 mg, 1.62 mmol, 3 mol equiv.) at 0 °C, and the mixture was stirred for 2 h at room temp. and then evaporated. The residue was chromatographed on a silica gel column [12 g; butanone–toluene (1 : 18, v/v)] to give the *isothiocyanate* **29** (154 mg, 95.8%) as a syrup (Found: C, 56.3; H, 6.6; N, 4.6. $C_{14}H_{19}NO_4S$ requires C, 56.55; H, 6.4; N, 4.7%); $[\alpha]_D^{30}$ +260 (*c* 1.31, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2060 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 5.50 (1 H, ddd, $J_{1,5a}$ 4.8, $J_{4,5a}$ 1.5, $J_{5a,6}$ 1.8, 5a-H), 4.61 (1 H, dd, $J_{1,2}$ 4.4, $J_{1,5a}$ 4.8, 1-H), 4.55 (1 H, ddd, $J_{3,4}$ 8.1, $J_{4,5a}$ 1.5, $J_{4,6a}$ 2.9, 4-H), 4.45 (1 H, ddd, $J_{4,6a}$ 2.9, $J_{5a,6a}$ 1.8, $J_{gem}$ 14.3, 6-H$^a$), 4.25 (1 H, d, $J_{gem}$ 14.3, 6-H$^b$), 4.04 (1 H, dd, $J_{2,3}$ 9.9, $J_{3,4}$ 8.1, 3-H), 3.62 (1 H, dd, $J_{1,2}$ 4.4, $J_{2,3}$ 9.9, 2-H) and 1.56, 1.51 and 1.45 (6, 3 and 3 H, 3 s, 2 × $CMe_2$).

### 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-α- 31α and -β-D-glucopyranosyl isothiocyanates 31β

2,2′,3,3′,4′,6,6′-Hepta-*O*-benzylmaltose[12] **30** (3.58 g, 3.68 mmol) was acetylated conventionally, and the product was purified on a silica gel column [40 g, EtOAc–hexane (1 : 4, v/v)] to give the acetate (3.70 g, 99.0%) as a syrup.

A portion (500 mg; 0.493 mmol) of the product was treated with KSCN as in the preparation of compound **18α,β** to give, first, the β-*isothiocyanate* **31β** (151 mg, 30.2%) as a syrup (Found: C, 73.1; H, 6.3; N, 1.3. $C_{62}H_{63}NO_{10}S$ requires C, 73.4; H, 6.3; N, 1.4%); $[\alpha]_D^{26}$ +2.6 (*c* 0.99, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2035 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.30–7.04 (35 H, m, 7 × Ph), 5.57 (1 H, d, $J_{1',2'}$ 3.7, 1′-H), 4.87–4.67 (7 H, m, 1-H and 3 × PhC$H_2$), 4.81 and 4.33 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.58 and 4.44 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.55 and 4.50 (each 1 H, ABq, $J_{gem}$ 11.6, PhC$H_2$), 4.54 and 4.47 (each 1 H, ABq, $J_{gem}$ 12.1, PhC$H_2$), 3.91–3.54 (11 H, m) and 3.48 (1 H, dd, $J_{1',2'}$ 3.7, $J_{2',3'}$ 9.9, 2′-H).

The second fractions gave the α-*isothiocyanate* **31α** (122 mg, 24.4%) as a syrup (Found: C, 73.2; H, 6.3; N, 1.4%); $[\alpha]_D^{26}$ +3.1 (*c* 0.98, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2035 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.32–7.05 (35 H, m, 7 × Ph), 5.64 (1 H, d, *J* 3.7, 1- or 1′-H), 5.44 (1 H, d, *J* 4.0, 1′- or 1-H), 4.97 and 4.80 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.90 and 4.80 (each 1 H, ABq, $J_{gem}$ 10.6, PhC$H_2$), 4.79 and 4.42 (each 1 H, ABq, $J_{gem}$ 10.8, PhC$H_2$), 4.66 and 4.59 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.61 and 4.54 (each 1 H, ABq, $J_{gem}$ 11.9, PhC$H_2$), 4.51 and 4.28 (each 1 H, ABq, $J_{gem}$ 12.3, PhC$H_2$), 4.48 and 4.43 (each 1 H, ABq, $J_{gem}$ 12.6, PhC$H_2$), 4.10–3.48 (9 H, m), 3.71 (1 H, dd, *J* 4.0 and 9.2, 2- or 2′-H), 3.50 (1 H, dd, *J* 3.7 and 9.7, 2′- or 2-H) and 3.38 (1 H, dd, *J* 1.3 and 9.6, 6- or 6′-H).

### 2,3,6-Tri-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-α- 33α and -β-D-glucopyranosyl isothiocyanates 33β

2,2′,3,3′,4′,6,6′-Hepta-*O*-benzylcellobiosyl acetate[13] **32** (380 mg, 0.374 mmol) was converted, as in the preparation of compounds **18α,β**, into the isothiocyanates through an intermediate chloride. Column chromatography of the products afforded, first, the β-*isothiocyanate* **33β** (140 mg, 37.3%) as crystals; mp 114–115 °C (from hexane) (Found: C, 73.3; H, 6.2; N, 1.35. $C_{62}H_{63}NO_{10}S$ requires C, 73.4; H, 6.3; N, 1.4%); $[\alpha]_D^{21}$ +28.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2040 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.34–7.12 (35 H, m, 7 × Ph), 5.13 and 4.69 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.90–4.39 (14 H, m, 1-, 1′-H and 6 × PhC$H_2$), 4.04 (1 H, dd, *J* 9.3 and 9.5), 3.81 (1 H, dd, *J* 3.3, $J_{gem}$ 11.0, 6- or 6′-H) and 3.71–3.25 (11 H, m).

The second fractions gave the α-*isothiocyanate* **33α** (80.0 mg, 21.3%) as a syrup (Found: C, 73.4; H, 6.3; N, 1.3%); $[\alpha]_D^{21}$ +66.7 (*c* 1.00, $CHCl_3$); $\nu_{max}$(neat)/cm$^{-1}$ 2040 (N=C=S); $\delta_H$(270 MHz; $CDCl_3$) 7.47–7.13 (35 H, m, 7 × Ph), 5.36 (1 H, d, $J_{1,2}$ 4.0, 1-H), 5.07 and 4.72 (each 1 H, ABq, $J_{gem}$ 11.4, PhC$H_2$), 4.91–4.33 (13 H, m, 1′-H, 6 × PhC$H_2$), 3.96 (1 H, dd, *J* 9.3 and 9.6), 3.83 (1 H, dd, *J* 2.8, $J_{gem}$ 11.2, 6- or 6′-H), 3.75–3.33 (9 H, m) and 3.28 (1 H, m, 5- or 5′-H).

### *N*-Phenyl-*N*′-[(1*R*)-(1,3,5/2,4)-2,3,4,5-tetrahydroxy-2-(hydroxymethyl)cyclopentyl]thiourea 34

A mixture of trehazolamine[4] **2** (23.2 mg, 0.129 mmol) and PhNCS **13** (52.3 mm$^3$, 0.387 mmol, 3 mol equiv.) in 60% aq. EtOH (1 cm$^3$) was stirred for 2 h at room temp., and then evaporated. The residue was eluted from a column of silica gel (1 g) with PhMe ⟶ EtOH–PhMe (1 : 3) to afford the *phenylthiourea* **34** (40.2 mg, 99.3%) as a powder (Found: C, 49.6; H, 6.05; N, 8.6. $C_{13}H_{18}N_2O_5S$ requires C, 49.7; H, 5.8; N, 8.9%); $[\alpha]_D^{25}$ +24.3 (*c* 2.01, MeOH); $\nu_{max}$(KBr)/cm$^{-1}$ 3415 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $D_2O$) 7.40–7.14 (5 H, m, Ph), 4.61 (1 H, d, $J_{1,5}$ 7.9, 1-H), 4.14 (1 H, ddd, $J_{1,5}$ 7.9, $J_{3,5}$ 2.2, $J_{4,5}$ 4.4, 5-H), 3.73–3.64 (2 H, m, 3- and 4-H) and 3.54 and 3.49 (each 1 H, ABq, $J_{gem}$ 12.6, $CH_2$OH).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-3-Anilino-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 3

A suspension of the phenylthiourea **34** (36.3 mg, 0.115 mmol) and yellow HgO (74.7 mg, 0.345 mmol, 3 mol equiv.) in acetone–EtOH (1 : 1, v/v) (2 cm$^3$) was vigorously stirred for 5 h at room temp. The mixture was filtered through a bed of Celite and the bed was washed with EtOH. The filtrate and washings

were evaporated and the residue was eluted from a column of Dowex 50W-X2 ($H^+$) resin (2 $cm^3$) with MeOH–28% aq. $NH_4OH$ (6:1, v/v) to afford the *phenylisourea* **3** (29.9 mg, 93.0%) as a hygroscopic powder (Found: C, 52.6; H, 6.4; N, 9.5. $C_{13}H_{16}N_2O_5 \cdot H_2O$ requires C, 52.3; H, 6.1; N, 9.4%); $[\alpha]_D^{26}$ +87.8 (*c* 1.31, MeOH); $\nu_{max}$(KBr)/$cm^{-1}$ 3405 (OH and NH) and 1640 (C=N); $\delta_H$(270 MHz; $D_2O$) 7.30–6.96 (5 H, m, Ph), 4.84 (1 H, ddd, $J_{1,5}$ 8.4, $J_{1,7}$ 1.3, $J_{1,8}$ 2.6, 1-H), 4.23 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.11 (1 H, dd, $J_{1,8}$ 2.6, $J_{7,8}$ 4.4, 8-H), 3.85 (1 H, dd, $J_{1,7}$ 1.3, $J_{7,8}$ 4.4, 7-H) and 3.74 and 3.63 (each 1 H, ABq, $J_{gem}$ 12.1, $CH_2OH$).

### *N*-Benzyl-*N'*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-tetrahydroxy-2-(hydroxymethyl)cyclopentyl]thiourea 35

Trehazolamine **2** (19.1 mg, 0.107 mmol) was allowed to couple with BnNCS **14** (47.9 $mm^3$, 0.321 mmol, 3 mol equiv.) as in the preparation of compound **34**, for 4 h at room temp. Chromatography of the product on silica gel (1 g) with PhMe ⟶ EtOH–PhMe (1:3, v/v) as eluent gave the *benzylthiourea* **35** (34.2 mg, 97.4%) as a solid (Found: C, 51.4; H, 6.5; N, 8.1. $C_{14}H_{20}N_2O_5S$ requires C, 51.2; H, 6.1; N, 8.5%); $[\alpha]_D^{25}$ +35.3 (*c* 1.89, MeOH); $\nu_{max}$(KBr)/$cm^{-1}$ 3410 (OH and NH) and 1550 (NH); $\delta_H$(270 MHz; $D_2O$) 7.34–7.16 (5 H, m, Ph), 4.80–4.26 (3 H, m, 1-H and PhC$H_2$), 4.05 (1 H, dd, $J_{1,5}$ 8.1, $J_{4,5}$ 4.8, 5-H) and 3.87–3.23 (4 H, m, 3- and 4-H and C$H_2$OH).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-3-Benzylamino-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 4

A solution of the benzylthiourea **35** (27.0 mg, 0.0822 mmol) in acetone–EtOH (1:1, v/v) (2 $cm^3$) was treated, as in the preparation of compound **3**, with yellow HgO (53.5 mg, 0.247 mmol, 3 mol equiv.) for 5 h at room temp. The product was purified by a column of Dowex 50W-X2 ($H^+$) resin (2 $cm^3$) with MeOH–28% aq. $NH_4OH$ (6:1, v/v) as eluent to afford the *benzylisourea* **4** (22.4 mg, 92.6%) as a hygroscopic powder (Found: C, 55.7; H, 6.4; N, 9.2. $C_{14}H_{18}N_2O_5 \cdot 0.5H_2O$ requires C, 55.4; H, 6.3; N, 9.2%); $[\alpha]_D^{26}$ +3 (*c* 1.1, MeOH); $\nu_{max}$(KBr)/$cm^{-1}$ 3420 (OH and NH) and 1655 (C=N); $\delta_H$(270 MHz; $D_2O$) 7.34–7.14 (5 H, m, Ph), 4.70 (1 H, dd, $J_{1,5}$ 8.8, $J_{1,8}$ 2.7, 1-H), 4.17 (2 H, s, PhC$H_2$), 4.12 (1 H, d, $J_{1,5}$ 8.8, 5-H), 3.95 (1 H, dd, $J_{1,8}$ 2.7, $J_{7,8}$ 5.5, 8-H), 3.75 (1 H, d, $J_{7,8}$ 5.5, 7-H) and 3.48 and 3.36 (each 1 H, ABq, $J_{gem}$ 12.1, C$H_2$OH).

### *N*-(2',3',4',6'-Tetra-*O*-acetyl-α-D-mannopyranosyl)-*N'*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-tetrahydroxycyclopentyl]-2-(hydroxymethyl)thiourea 36

Trehazolamine[4] **2** (19.9 mg, 0.111 mmol) was allowed to couple with the α-mannopyranosyl isothiocyanate **16α** (61.0 mg, 0.157 mmol, 1.4 mol equiv.) in 75% aq. THF (2 $cm^3$) for 30 min at room temp. The product was chromatographed on a column of silica gel (2 g) with PhMe ⟶ EtOH–PhMe (1:4, v/v) as eluent to afford the *thiourea* **36** (46.0 mg, 72.9%) as a hygroscopic syrup (Found: C, 43.6; H, 5.9; N, 4.7. $C_{21}H_{32}N_2O_{14}S \cdot 0.5H_2O$ requires C, 43.7; H, 5.8; N, 4.85%); $[\alpha]_D^{25}$ +79 (*c* 1.42, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3340 (OH and NH), 1750 (OAc) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 8.11 (1 H, br s, NH or N'H), 7.70 (1 H, br s, N'H or NH), 5.96–5.25 (6 H, m, 1'-, 2'-, 3'- and 4'-H and 2 × OH), 4.84 (1 H, br s, 1-H), 4.35–4.03 (7 H, m), 3.91 (1 H, br s), 3.66 (1 H, br s), 2.81 (2 H, br s, 2 × OH) and 2.18, 2.09, 2.05 and 2.00 (each 3 H, 4 s, 4 × Ac).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(2',3',4',6'-tetra-*O*-acetyl-α-D-mannopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]-oct-3-ene-6,7,8-triol 44

To a solution of the thiourea **36** (48.5 mg, 0.0850 mmol) in EtOH–acetone (1:1, v/v) (2 $cm^3$) was added yellow HgO (55.2 mg, 0.255 mmol, 3 mol equiv.) at room temp. The mixture was stirred for 1.5 h at the same temp. after which it was filtered through a bed of Celite, which was thoroughly washed with EtOH. The filtrate and washings were evaporated to afford the *cyclic isourea* **44** (45.6 mg, 100%) as a hygroscopic syrup (Found: C, 45.2; H, 6.3; N, 4.85. $C_{21}H_{30}N_2O_{14} \cdot H_2O$ requires C, 45.65; H, 5.8; N, 5.1%); $[\alpha]_D^{24}$ +57.7 (*c* 1.32, $CHCl_3$); $\nu_{max}$(neat)/ $cm^{-1}$ 3360 (OH and NH), 1740 (OAc) and 1670 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.43–4.91 (6 H, m, 1'-, 2'-, 3'-, 4'-, 1- and 5-H), 4.45–3.80 (11 H, m), 2.76 (1 H, br s, OH) and 2.15, 2.10, 2.04 and 1.99 (each 3 H, 4 s, 4 × Ac).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(α-D-mannopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (2'-*epi*-trehazolin) 5

The isourea **44** (14.8 mg, 0.0277 mmol) was treated with methanolic NaOMe in MeOH (1 $cm^3$) for 30 min at −20 °C. The product was purified by a column of Dowex 50W-X2 ($H^+$) resin (2 $cm^3$) with 0.5 mol $dm^{-3}$ aq. $NH_4OH$ as eluent to give 2'-*epi*-trehazolin **5** (7.3 mg, 72.3%) as a powder; $[\alpha]_D^{24}$ +107 (*c* 0.37, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3390 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$) 5.04 (1 H, d, $J_{1',2'}$ 2.7, 1'-H), 4.84 (1 H, dd, $J_{1,5}$ 8.4, $J_{1,8}$ 3.0, 1-H), 4.22 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.07 (1 H, dd, $J_{1,8}$ 3.0, $J_{7,8}$ 3.7, 8-H), 3.85–3.38 (7 H, m, 2'-, 3'- and 5'-H and 6'-$H_2$, C$H_2$OH), 3.82 (1 H, d, $J_{7,8}$ 3.7, 7-H) and 3.52 (1 H, dd, $J_{3',4'}$ 9.3, $J_{4',5'}$ 9.3, 4'-H).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-3-(2',3',4',6'-tetra-*O*-acetyl-α-D-mannopyranosylimino)-4-*N*,7-*O*,8-*O*-triacetyl-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 5a

Conventional acetylation of the isourea **5** (6.8 mg, 0.0187 mmol) gave, after chromatography on silica gel (1 g) with acetone–PhMe (2:5, v/v) as eluent, the *octa*-N,O-*acetyl derivative* **5a** (10.7 mg, 81.7%) as a syrup (Found: C, 49.6; H, 5.7; N, 3.9. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.45; N, 4.0%); $[\alpha]_D^{23}$ +78 (*c* 0.54, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1750 (OAc) and 1690 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.56 (2 H, d, *J* 1.8, 7- and 8-H), 5.42 (1 H, d, $J_{1',2'}$ 2.2, 1'-H), 5.35 (1 H, dd, $J_{3',4'}$ 9.4, $J_{4',5'}$ 10.3, 4'-H), 5.28 (1 H, dd, $J_{2',3'}$ 2.6, $J_{3',4'}$ 9.4, 3'-H), 5.10 (1 H, dd, $J_{1',2'}$ 2.2, $J_{2',3'}$ 2.6, 2'-H), 4.95 (1 H, ddd, $J_{1,5}$ 10.0, $J_{1,7}$ 1.8, $J_{1,8}$ 1.8, 1-H), 4.87 (1 H, d, $J_{1,5}$ 10.0, 5-H), 4.32–4.27 (1 H, m, 5'-H), 4.22 (1 H, dd, $J_{5',6'}$ 8.3, $J_{gem}$ 13.8, 6'-H), 4.15 and 3.89 (each 1 H, ABq, $J_{gem}$ 11.7, C$H_2$OH), 4.11 (1 H, dd, $J_{5',6'}$ 4.4, $J_{gem}$ 13.8, 6'-H), 3.75 (1 H, s, OH) and 2.63, 2.18, 2.12, 2.11, 2.10, 2.09, 2.06 and 1.99 (each 3 H, 8 s, 8 × Ac).

### *N*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)-cyclopentyl]-*N'*-(2,4,6-tri-*O*-benzyl-3-deoxy-α-D-*ribo*-hexopyranosyl)thiourea 37

Trehazolamine **2** (18.2 mg, 0.102 mmol) was allowed to couple with the 3-deoxy-α-D-*ribo*-hexopyranosyl isothiocyanate **18α** (72.8 mg, 0.153 mmol, 1.5 mol equiv.) in 75% aq. THF for 40 h at room temp. The product was chromatographed on a column of silica gel (4 g) with EtOAc–hexane (1:5, v/v) ⟶ EtOH–PhMe (1:5, v/v) as eluent to give the *thiourea* **37** (60.8 mg, 91.0%) as a syrup (Found: C, 61.9; H, 6.8; N, 4.3. $C_{34}H_{42}N_2O_9S$ requires C, 62.4; H, 6.5; N, 4.3%); $[\alpha]_D^{23}$ +160 (*c* 1.0, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3325 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.78 (1 H, d, $J_{1,NH}$ 4.9, NH), 7.36–7.12 (15 H, m, 3 × Ph), 5.72 (1 H, br s, N'H), 5.31 (1 H, br s, 1'-H), 4.76–3.43 (20 H, m), 2.36 (1 H, br s, 3-$H^{eq}$) and 2.12 (1 H, s, OH) and 1.62 (1 H, ddd, *J* 11.3, 11.9 and 12.0, 3-$H^{ax}$). The signal due to one OH group was not observed.

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(2',4',6'-tri-*O*-benzyl-3-deoxy-α-D-*ribo*-hexopyranosylamino)-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol 45

The thiourea **37** (60.8 mg, 0.0929 mmol) was treated with yellow HgO (60.4 mg, 0.279 mmol, 3 mol equiv.) in diethyl ether (10 $cm^3$) for 4 h at room temp., and then, after each 4 and 7 h,

additional HgO (each 60.4 mg, 0.279 mmol, 3 mol equiv.; total 181 mg, 0.837 mmol, 9 mol equiv.) was added to the reaction mixture. The mixture was stirred for 14 h at the same temp. and then was filtered through a bed of Celite, which was washed with EtOH. The filtrate and washings were evaporated to afford the *isourea* **45** (57.7 mg, 100%) as a syrup (Found: C, 65.35; H, 6.9; N, 4.3. $C_{34}H_{40}N_2O_9$ requires C, 65.8; H, 6.5; N, 4.5%); $[\alpha]_D^{24}$ +72.9 (*c* 1.07, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3350 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 7.38–7.14 (m, 15 H, 3 × Ph), 5.35 (1 H, d, $J_{1',2'}$ 3.9, 1'-H), 4.76 (1 H, d, $J_{1,5}$ 7.4, 1-H), 4.54–4.26 (8 H, m), 3.90–3.28 (9 H, m), 2.33 (1 H, br s, 3-$H^{eq}$) and 1.65 (1 H, ddd, *J* 11.6, 11.9 and 12.0, 3-$H^{ax}$). The signals due to three OH groups and one NH group were not observed.

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-(3'-Deoxy-α-D-*ribo*-hexopyranosylamino)-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (3'-deoxytrehazolin) 6**

To a mixture of sodium (104 mg, 4.52 mmol, 100 mol equiv.) and liquid ammonia (5 $cm^3$) was added a solution of the isourea **45** (27.8 mg, 0.0448 mmol) in THF (2 $cm^3$) at −78 °C. The mixture was stirred for 15 min at −78 °C. After addition of $NH_4Cl$ (361 mg, 6.75 mmol, 150 mol equiv.), ammonia was removed by spontaneous evaporation at room temp. and the residue was eluted from a column of Dowex 50W-X2 ($H^+$) resin (20 $cm^3$) with 0.125 mol $dm^{-3}$ aq. $NH_4OH$ as eluent to give 3'-deoxytrehazolin **6** (12.8 mg, 80.5%) as a powder, $[\alpha]_D^{22}$ +114 (*c* 0.64, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3400 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$) 5.11 (1 H, d, $J_{1',2'}$ 5.1, 1'-H), 4.83 (1 H, dd, $J_{1,5}$ 8.8, $J_{1,8}$ 2.4, 1-H), 4.23 (1 H, d, $J_{1,5}$ 8.8, 5-H), 4.07 (1 H, dd, $J_{1,8}$ 2.4, $J_{7,8}$ 4.4, 8-H), 3.86 (1 H, ddd, $J_{1',2'}$ 5.1, $J_{2',3'ax}$ 12.1, $J_{2',3'eq}$ 4.8, 2'-H), 3.81 (1 H, d, $J_{7,8}$ 4.4, 7-H), 3.67 and 3.57 (each 1 H, ABq, $J_{gem}$ 12.1, $CH_2OH$), 3.65 (1 H, dd, $J_{5',6'a}$ 2.6, $J_{gem}$ 12.3, 6'-$H^a$), 3.56 (1 H, dd, $J_{5',6'b}$ 6.6, $J_{gem}$ 12.3, 6'-$H^b$), 3.50 (1 H, ddd, $J_{3'eq,4'}$ 5.4, $J_{3'ax,4'}$ 11.4, $J_{4',5'}$ 9.5, 4'-H), 3.30 (1 H, ddd, $J_{4',5'}$ 9.5, $J_{5',6'}$ 2.6 and 6.6, 5'-H), 2.11 (1 H, ddd, $J_{2',3'eq}$ 4.8, $J_{3'eq,4'}$ 5.4, $J_{gem}$ 11.6, 3'-$H^{eq}$) and 1.51 (1 H, ddd, $J_{2',3'ax}$ 12.1, $J_{3'ax,4'}$ 11.4, $J_{gem}$ 11.6, 3'-$H^{ax}$).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-(2',4',6'-tri-*O*-acetyl-3'-deoxy-α-D-*ribo*-hexopyranosylimino)-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 6a**

The free base **6** (12.8 mg, 0.0362 mmol) was acetylated conventionally to give, after chromatography on silica gel [2 g, (1:5) acetone–PhMe], the *hepta*-N,O-*acetyl derivative* **6a** (16.4 mg, 70.7%) as a syrup (Found: C, 50.59; H, 5.71; N, 4.08. $C_{27}H_{36}N_2O_{16}$ requires C, 50.31; H, 5.63; N, 4.35%); $[\alpha]_D^{20}$ +121 (*c* 0.55, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1745 (OAc) and 1695 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.55 (1 H, d, $J_{7,8}$ 8.8, 7-H), 5.50 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.8, 8-H), 5.49 (1 H, d, $J_{1',2'}$ 4.4, 1'-H), 5.04 (1 H, ddd, $J_{1',2'}$ 4.4, $J_{2',3'eq}$ 5.1, $J_{2',3'ax}$ 12.1, 2'-H), 4.89 (1 H, d, $J_{1,5}$ 9.9, 5-H), 4.87–4.81 (1 H, m, 4'-H), 4.80 (1 H, dd, $J_{1,5}$ 9.9, $J_{1,8}$ 3.3, 1-H), 4.17 and 3.93 (each 1 H, ABq, $J_{gem}$ 11.7, $CH_2OAc$), 4.15–4.11 (3 H, m, 5'-H and 6'-$H_2$), 3.77 (1 H, s, OH), 2.64, 2.107, 2.105, 2.10, 2.06 and 1.98 (3, 3, 3, 6, 3 and 3 H, 6 s, 7 × Ac), 2.25 (1 H, ddd, $J_{2',3'eq}$ 5.1, $J_{3'eq,4'}$ 5.5, $J_{gem}$ 10.6, 3'-$H^{eq}$) and 1.83 (1 H, ddd, $J_{2',3'ax}$ 12.1, $J_{3'ax,4'}$ 11.5, $J_{gem}$ 10.6, 3'-$H^{ax}$).

***N*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-*N'*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-tetrahydroxy-2-hydroxymethylcyclopentyl]-thiourea 38**

Trehazolamine **2** (20.1 mg, 0.112 mmol) was allowed to react with the α-galactopyranosyl isothiocyanate **20a** (94.8 mg, 0.163 mmol, 1.5 mol equiv.) in 75% aq. THF (2 $cm^3$) for 22 h at room temp. The product was chromatographed on a column of silica gel (3 g) with EtOAc–hexane (1:3, v/v) ⟶ EtOH–PhMe (1:5, v/v) as eluent to give the *thiourea* **38** (74.5 mg, 87.2%) as a syrup (Found: C, 64.3; H, 6.6; N, 3.5. $C_{41}H_{48}N_2O_{10}S$ requires C, 64.7; H, 6.4; N, 3.7%); $[\alpha]_D^{26}$ +109 (*c* 1.30, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3300 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.78 (1 H, br s, N'H), 7.40–7.10 (20 H, m, 4 × Ph), 5.88 (1 H, br s, NH), 5.33 (1 H, br s), 4.80 and 4.29 (each 1 H, ABq, $J_{gem}$ 11.8, PhC$H_2$), 4.75–4.38 (6 H, m), 4.70 and 4.61 (each 1 H, ABq, $J_{gem}$ 11.6, PhC$H_2$) and 4.13–3.30 (10 H, m).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]-oct-3-ene-6,7,8-triol 46**

The thiourea **38** (74.5 mg, 0.0980 mmol) was treated with four portions of yellow HgO (each 63.6 mg, 0.294 mmol, 3 mol equiv.; total 254 mg, 1.18 mmol, 12 mol equiv.), in similar manner to that in the preparation of compound **45**, to give the *isourea* **46** (70.8 mg, ~100%) as a syrup (Found: C, 67.3; H, 6.6; N, 3.6. $C_{41}H_{46}N_2O_{10}$ requires C, 67.75; H, 6.4; N, 3.85%); $[\alpha]_D^{24}$ +52.3 (*c* 1.38, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3350 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.10 (20 H, m, 4 × Ph), 5.36 (1 H, br s, 1'-H), 4.89–4.14 (8 H, m), 4.84 and 4.46 (each 1 H, ABq, $J_{gem}$ 11.6, PhC$H_2$), 4.73 and 4.64 (each 1 H, ABq, $J_{gem}$ 11.7, PhC$H_2$), 4.41 and 4.29 (each 1 H, ABq, $J_{gem}$ 11.0, PhC$H_2$), 4.07 (1 H, dd, $J_{1',2'}$ 5.1, $J_{2',3'}$ 10.3, 2'-H), 3.90–3.28 (8 H, m) and 3.68 (1 H, br s, 3'-H).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-(α-D-Galactopyranosylamino)-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (4'-*epi*-trehazolin) 7**

O-Debenzylation of the isourea **46** (31.9 mg, 0.0440 mmol) was carried out as in the preparation of compound **6** to give 4'-*epi*-trehazolin **7** (12.8 mg, 79.5%) as a powder, $[\alpha]_D^{24}$ +124 (*c* 0.64, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3410 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$) 5.22 (1 H, d, $J_{1',2'}$ 5.5, 1'-H), 4.80 (1 H, dd, $J_{1,5}$ 8.4, $J_{1,8}$ 2.8, 1-H), 4.21 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.07 (1 H, dd, $J_{1,8}$ 2.8, $J_{7,8}$ 4.4, 8-H), 3.87 (1 H, dd, $J_{1',2'}$ 5.5, $J_{2',3'}$ 10.6, 2'-H), 3.83–3.51 (5 H, m, 3'-, 4'- and 5'-H and 6'-$H_2$), 3.80 (1 H, d, $J_{7,8}$ 4.4, 7-H) and 3.67 and 3.57 (each 1 H, ABq, $J_{gem}$ 11.7, $CH_2OH$).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-(2',3',4',6'-tetra-*O*-acetyl-α-D-galactopyranosylimino)-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 7a**

The free base **7** (10.3 mg, 0.0281 mmol) was acetylated conventionally to give, after chromatography on silica gel (2 g) with acetone–PhMe (2:7, v/v) as eluent, the *octa*-N,O-*acetyl derivative* **7a** (18.5 mg, 93.4%) as a syrup (Found: C, 50.0; H, 5.6; N, 4.1. $C_{29}H_{38}N_2O_{18}$ requires C, 49.6; H, 5.45; N, 4.0%); $[\alpha]_D^{23}$ +98.5 (*c* 0.93, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1750 (OAc) and 1690 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.65 (1 H, d, $J_{1',2'}$ 4.0, 1'-H), 5.55 (1 H, d, $J_{7,8}$ 8.0, 7-H), 5.47 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.0, 8-H), 5.46 (1 H, dd, $J_{3',4'}$ 3.1, $J_{4',5'}$ 1.8, 4'-H), 5.34 (1 H, dd, $J_{1',2'}$ 4.0, $J_{2',3'}$ 11.0, 2'-H), 5.25 (1 H, dd, $J_{2',3'}$ 11.0, $J_{3',4'}$ 3.1, 3'-H), 4.89 (1 H, d, $J_{1,5}$ 9.9, 5-H), 4.79 (1 H, dd, $J_{1,5}$ 9.9, $J_{1,8}$ 3.3, 1-H), 4.52 (1 H, ddd, $J_{4',5'}$ 1.8, $J_{5',6'a}$ 6.2, $J_{5',6'b}$ 7.0, 5'-H), 4.16 (1 H, dd, $J_{5',6'a}$ 6.2, $J_{gem}$ 11.4, 6'-$H^a$), 4.14 and 3.90 (each 1 H, ABq, $J_{gem}$ 11.4, $CH_2OH$), 3.98 (1 H, dd, $J_{5',6'b}$ 7.0, $J_{gem}$ 11.4, 6'-$H^b$), 3.77 (1 H, s, OH) and 2.62, 2.16, 2.11, 2.09, 2.08, 2.07, 1.99 and 1.98 (each 3 H, 8 s, 8 × Ac).

***N*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)-cyclopentyl]-*N'*-(2',3',4'-tri-*O*-benzyl-6'-deoxy-α-D-glucopyranosyl)thiourea 39**

Trehazolamine **2** (24.0 mg, 0.134 mmol) was treated with the isothiocyanate **24α** (82.8 mg, 0.174 mmol, 1.3 mol equiv.) in 75% aq. THF (2 $cm^3$) for 22 h at room temp. The product was eluted from a column of silica gel (4 g) with EtOAc–hexane (1:6, v/v) ⟶ EtOH–PhMe (1:5, v/v) as eluent to afford the *thiourea* **39** (80.0 mg, 91.2%) as a syrup (Found: C, 61.9; H, 6.7; N, 4.2. $C_{34}H_{42}N_2O_9S$ requires C, 62.4; H, 6.5; N, 4.3%); $[\alpha]_D^{25}$ +156

(*c* 1.08, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3320 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.85 (1 H, d, $J_{1,NH}$ 5.6, NH), 7.35–7.18 (15 H, m, 3 × Ph), 6.19 (1 H, br s, N'H), 5.34 (1 H, br s, 1'-H), 4.86–3.08 (18 H, m), 2.38 (1 H, s, OH) and 1.22 (3 H, d, $J_{5,6}$ 5.9, Me). The signals due to two OH groups were not observed.

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(2',3',4'-tri-*O*-benzyl-6'-deoxy-α-D-glucopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]-oct-3-ene-6,7,8-triol 47**

The thiourea **39** (80.0 mg, 0.122 mmol) was treated with three portions of yellow HgO (each 79.3 mg, 0.366 mmol, 3 mol equiv.; total 238 mg, 1.11 mmol, 9 mol equiv.), as in the preparation of compound **45**, to give the *isourea* **47** (74.3 mg, 98.2%) as a syrup (Found: C, 65.4; H, 6.9; N, 4.6. $C_{34}H_{40}N_2O_9S$ requires C, 65.8; H, 6.5; N, 4.5%); $[\alpha]_D^{24}$ +62.9 (*c* 1.12, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3360 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.10 (15 H, m, 3 × Ph), 5.34 (1 H, br s, 1'-H), 4.90–4.45 (10 H, m, 1-H, 3 × PhC$H_2$ and 3 × OH), 4.36 (1 H, d, $J_{1,5}$ 8.1, 5-H), 4.03–3.07 (9 H, m) and 1.19 (3 H, d, $J_{5,6}$ 5.9, Me). The signal due to one OH group was not observed.

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-(6'-Deoxy-α-D-glucopyranosylamino)-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (6'-deoxytrehazolin) 8**

O-Debenzylation of the isourea **47** (74.3 mg, 0.120 mmol) gave, as in the preparation of compound **7**, 6'-deoxytrehazolin **8** (33.1 mg, 78.1%) as a powder; $[\alpha]_D^{26}$ +102 (*c* 1.75, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3430 (OH and NH) and 1615 (C=N); $\delta_H$(270 MHz; $D_2O$) 5.14 (1 H, d, $J_{1',2'}$ 5.1, 1'-H), 4.77 (1 H, dd, $J_{1,5}$ 8.2, $J_{1,8}$ 2.0, 1-H), 4.19 (1 H, d, $J_{1,5}$ 8.2, 5-H), 4.03 (1 H, dd, $J_{1,8}$ 2.0, $J_{7,8}$ 4.8, 8-H), 3.80 (1 H, d, $J_{7,8}$ 4.8, 7-H), 3.66 and 3.56 (each 1 H, ABq, $J_{gem}$ 11.9, C$H_2$OH), 3.61 (1 H, dd, $J_{1',2'}$ 5.1, $J_{2',3'}$ 9.3, 2'-H), 3.50 (1 H, dq, $J_{4',5'}$ 9.5, $J_{5',6'}$ 5.9, 5'-H), 3.45 (1 H, dd, $J_{2',3'}$ 9.3, $J_{3',4'}$ 8.8, 3'-H), 2.99 (1 H, dd, $J_{3',4'}$ 8.8, $J_{4',5'}$ 9.5, 4'-H) and 1.08 (3 H, d, $J_{5',6'}$ 5.9, Me).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-(2',3',4'-tri-*O*-acetyl-6'-deoxy-α-D-glucopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 8a**

Conventional acetylation of the free base **8** (30.0 mg, 0.0850 mmol) gave the *hepta*-N,O-*acetyl derivative* **8a** (52.5 mg, 95.8%) as a syrup (Found: C, 50.4; H, 5.7; N, 4.0. $C_{27}H_{36}N_2O_{16}$ requires C, 50.3; H, 5.6; N, 4.35%); $[\alpha]_D^{23}$ +109 (*c* 2.55, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1745 (OAc) and 1695 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.53 (1 H, d, $J_{7,8}$ 8.8, 7-H), 5.52 (1 H, d, $J_{1',2'}$ 4.4, 1'-H), 5.47 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.8, 8-H), 5.35 (1 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.9, 3'-H), 5.03 (1 H, dd, $J_{1',2'}$ 4.4, $J_{2',3'}$ 10.3, 2'-H), 4.89 (1 H, d, $J_{1,5}$ 9.5, 5-H), 4.81 (1 H, dd, $J_{3',4'}$ 9.9, $J_{4',5'}$ 9.9, 4'-H), 4.79 (1 H, dd, $J_{1,5}$ 9.5, $J_{1,8}$ 3.3, 1-H), 4.18 and 3.88 (each 1 H, ABq, $J_{gem}$ 11.7, C$H_2$OH), 4.16 (1 H, dq, $J_{4',5'}$ 9.9, $J_{5',6'}$ 5.5, 5'-H), 3.77 (1 H, s, OH), 2.67, 2.10, 2.09, 2.08, 2.05, 1.99 and 1.97 (each 3 H, 7 s, 7 × Ac) and 1.16 (3 H, d, $J_{5',6'}$ 5.5, Me).

***N*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)-cyclopentyl]-*N'*-(2',3',4',6'-tetra-*O*-benzyl-5a'-carba-α-D-glucopyranosyl)thiourea 40**

Trehazolamine **2** (21.7 mg, 0.121 mmol) was allowed to couple with the isothiocyanate **27** (91.3 mg, 0.157 mmol, 1.3 mol equiv.) in 75% aq. THF (3 $cm^3$) for 5 days at room temp. The product was eluted from a column of silica gel (10 g) with EtOAc–hexane (1:3, v/v) ⟶ EtOH–PhMe (1:15, v/v) as eluent to afford the *thiourea* **40** (57.0 mg, 62.0%) as a syrup (Found: C, 66.2; H, 6.9; N, 3.45. $C_{42}H_{50}N_2O_9S$ requires C, 66.5; H, 6.6; N, 3.7%); $[\alpha]_D^{26}$ +78.7 (*c* 2.14, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3300 (OH and NH) and 1590 and 1550 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.86 (1 H, br s, NH), 7.33–7.11 (20 H, m, 4 × Ph), 6.65 (1 H, br s, NH), 5.07–4.30 (13 H, m, 1- and 1'-H, 3 × OH and 4 × PhC$H_2$), 4.00–3.32 (10 H, m) and 2.18–1.43 (5 H, m, 5'-H, 5a'-$H_2$ and 2 × OH).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-(2',3',4',6'-tetra-*O*-benzyl-5a'-carba-α-D-glucopyranosylamino)-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 48**

The thiourea **40** was treated, as in the preparation of compound **45**, with three portions of yellow HgO (each 44.8 mg, 0.207 mmol, 3 mol equiv.; total 134 mg, 0.621 mmol, 9 mol equiv.) to give the *cyclic isourea* **48** (48.3 mg, 96.6%) as a syrup (Found: C, 69.2; H, 6.7; N, 3.5. $C_{42}H_{48}N_2O_9$ requires C, 69.6; H, 6.7; N, 3.9%); $[\alpha]_D^{24}$ +44.5 (*c* 1.04, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3350 (OH and NH), 1660 (C=NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.30–7.14 (20 H, m, 4 × Ph), 4.92–3.47 (24 H, m), 3.66 (1 H, dd, $J_{3',4'} = J_{4',5'}$ = 9.5, 4'-H), 2.27 (1 H, br d, $J_{gem}$ 14.7, 5a'-$H^{eq}$), 1.93 (1 H, br dd, $J_{4',5'}$ 9.5, $J_{5',5a'\text{-ax}}$ 13.9, 5'-H) and 1.31 (1 H, br dd, $J_{5',5a'\text{-ax}}$ 13.9, $J_{gem}$ 14.7, 5a'-$H^{ax}$).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-(5a'-Carba-α-D-glucopyranosylamino)-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol (5a'-carbatrehazolin) 9**

O-Debenzylation of the isourea **48** (48.3 mg, 0.0666 mmol) was carried out as in the preparation of compound **7**, to give the carbatrehazolin **9** (24.3 mg, 100%) as a powder; $[\alpha]_D^{24}$ +62 (*c* 0.53, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3380 (OH and NH) and 1700 and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$) 4.96 (1 H, dd, $J_{1,5}$ 8.4, $J_{1,8}$ 1.7, 1-H), 4.28 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.13 (1 H, dd, $J_{1,8}$ 1.7, $J_{7,8}$ 4.4, 8-H), 3.93 (1 H, ddd, $J_{1',2'} = J_{1',5a'\text{-eq}} = J_{1',5a'\text{-ax}}$ 3.7, 1'-H), 3.84 (1 H, d, $J_{7,8}$ 4.4, 7-H), 3.67 (1 H, d, $J_{gem}$ 12.1, C$H_2$OH), 3.64–3.51 (3 H, m, 6'-$H_2$ and CH*H*OH), 3.48 (1 H, dd, $J_{1',2'}$ 3.7, $J_{2',3'}$ 8.9, 2'-H), 3.33 (1 H, dd, $J_{2',3'}$ 8.9, $J_{3',4'}$ 10.3, 3'-H), 3.15 (1 H, dd, $J_{3',4'}$ 10.3, $J_{4',5'}$ 8.8, 4'-H), 1.77 (1 H, ddd, $J_{1',5a'\text{-eq}}$ 2.5, $J_{5',5a'\text{-eq}}$ 3.7, $J_{gem}$ 13.9, 5a'-$H^{eq}$), 1.66–1.53 (1 H, m, 5'-H) and 1.39 (1 H, ddd, $J_{1',5a'\text{-ax}}$ 3.7, $J_{5',5a\text{-ax}}$ 10.9, $J_{gem}$ 13.9, 5a'-$H^{ax}$).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-(2',3',4',6'-tetra-*O*-acetyl-5a'-carba-α-D-glucopyranosylimino)-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 9a**

Acetylation of the carbatrehazolin **9** (20.7 mg, 0.0568 mmol) gave, after chromatography on silica gel (2 g) with acetone–PhMe (1:3, v/v), the *octa*-N,O-*acetyl derivative* **9a** (30.8 mg, 77.4%) as a syrup (Found: C, 51.65; H, 6.0; N, 3.9. $C_{30}H_{40}N_2O_{17}$ requires C, 51.4; H, 5.75; N, 4.0%); $[\alpha]_D^{24}$ +109 (*c* 1.02, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1750 (OAc) and 1690 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.51 (1 H, d, $J_{7,8}$ 8.4, 7-H), 5.43 (1 H, dd, $J_{2',3'}$ 10.2, $J_{3',4'}$ 9.7, 3'-H), 5.40 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.4, 8-H), 5.03 (1 H, dd, $J_{3',4'}$ 9.7, $J_{4',5'}$ 11.0, 4'-H), 4.93 (1 H, dd, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10.2, 2'-H), 4.87 (1 H, d, $J_{1,5}$ 9.7, 5-H), 4.75 (1 H, dd, $J_{1,5}$ 9.7, $J_{1,8}$ 3.3, 1-H), 4.28 (1 H, ddd, $J_{1',2'} = J_{1',5a'\text{-eq}} = J_{1',5a'\text{-ax}}$ 3.5, 1'-H), 4.26 and 3.91 (each 1 H, ABq, $J_{gem}$ 11.7, C$H_2$OAc), 4.12 (1 H, dd, $J_{5',6'a}$ 4.8, $J_{gem}$ 11.4, 6'-$H^a$), 3.90 (1 H, dd, $J_{5',6'b}$ 3.0, $J_{gem}$ 11.4, 6'-$H^b$), 3.85 (1 H, s, OH), 2.67, 2.11, 2.08, 2.06, 2.04, 2.03, 1.98 and 1.97 (each 3 H, 8 s, 8 × Ac), 2.49–2.36 (1 H, m, 5'-H) and 1.80–1.65 (2 H, m, 5a'-$H_2$).

***N*-[2',3':4'6'-Di-*O*-isopropylidene-5a'-carba-α-D-*xylo*-hex-5(5a)-enopyranosyl]-*N'*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-tetrahydroxy-2-(hydroxymethyl)cyclopentyl]thiourea 41**

A mixture of trehazolamine **2** (11.0 mg, 0.0614 mmol), the isothiocyanate **29** (23.6 mg, 0.0794 mmol) and aq. 75% THF (1 $cm^3$) was stirred for 20 h at room temp., and then was evaporated. The residue was chromatographed [(2.5 g); toluene ⟶ EtOH–toluene (1:8, v/v)] to give the *thiourea* **41** (26.4 mg, 95.2%) as a hygroscopic syrup (Found: C, 49.7; H, 7.2; N, 5.4. $C_{20}H_{30}N_2O_9 \cdot 0.5H_2O$ requires C, 49.5; H, 6.85; N, 5.8%); $[\alpha]_D^{28}$ +162 (*c* 1.32, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3360 (NH and OH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 8.14 (1 H, br s,

NH or N'H), 6.87 (1 H, br s, NH or N'H), 5.92–3.45 (14 H, m), 3.18–2.93 (2 H, m, 2 × OH) and 1.57, 1.47 and 1.41 (3, 6 and 3 H, 3 s, 2 × $CMe_2$).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-[2',3':4',6'-Di-*O*-isopropylidene-5a'-carba-α-D-*xylo*-hex-5(5a)-enopyranosylamino]-6-hydroxymethyl-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 49**

To a solution of compound **41** (11.2 mg, 0.0235 mmol) in diethyl ether (1.5 $cm^3$) was added yellow HgO (15.3 mg, 0.071 mmol), and the mixture was stirred for 3 h at room temp.; subsequently two further portions of HgO were added to the mixture after 3 h and 6 h. After 22 h the mixture was filtered through a Celite bed, which was thoroughly washed with ethanol. The filtrate and washings were combined and evaporated to give the *isourea* **49** (10.2 mg, 98.1%) as a syrup (Found: C, 54.85; H, 6.35; N, 6.0. $C_{20}H_{30}N_2O_9$ requires C, 54.3; H, 6.8; N, 6.3%); $[\alpha]_D^{24}$ +56 (*c* 0.51, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3340 (NH and OH), 1660 (C=N) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 5.61 (1 H, br s, 5-H[a]), 4.93–4.76 (1 H, br s, OH), 4.62–3.56 (12 H, m) and 1.56, 1.46, 1.43 and 1.41 (each 3 H, 4 s, 2 × $CMe_2$). The signals of three OH groups were not observed.

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-[5a'-Carba-α-D-*xylo*-hex-5(5a)-enopyranosylamino]-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol [5a'-carb-5'(5a')-enotrehazolin] 10**

A solution of the diacetonide **49** (10.2 mg, 0.023 mmol) and aq. 60% acetic acid (2 $cm^3$) was stirred for 2 h at 50 °C, and was then evaporated. The residue was purified by a column of Dowex 50W-X2 ($H^+$) resin with aq. 0.5 mol $dm^{-3}$ ammonia as eluent to give the isourea **10** (7.8 mg, 93%) as a solid, $[\alpha]_D^{26}$ +109 (*c* 0.39, water); $\delta_H$(270 MHz; $D_2O$) 5.98 (1 H, d, $J_{1',5a'}$ 5.1, 5a'-H), 4.79 (1 H, dd, $J_{1,5}$ 8.8, $J_{1,8}$ 2.9, 1-H), 4.26 (1 H, dd, $J_{1',2'}$ 5.1, $J_{1',5a'}$ 5.1, 1'-H), 4.20 (1 H, d, $J_{1,5}$ 8.8, 5-H), 4.08 and 3.99 (each 1 H, ABq, $J_{gem}$ 12.3, 6'-$H_2$), 4.06 (1 H, dd, $J_{1,8}$ 2.9, $J_{7,8}$ 5.9, 8-H), 3.95 (1 H, d, $J_{3',4'}$ 7.3, 4'-H), 3.79 (1 H, d, $J_{7,8}$ 5.9, 7-H), 3.65 and 3.56 (each 1 H, ABq, $J_{gem}$ 12.3, C$H_2$OH), 3.64 (1 H, dd, $J_{1',2'}$ 5.1, $J_{2',3'}$ 10.3, 2'-H) and 3.46 (1 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 7.3, 3'-H).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-[2',3',4',6'-tetra-*O*-acetyl-5a'-carba-α-D-*xylo*-hex-5(5a)-enopyranosylamino]-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 10a**

The isourea **10** (5.0 mg, 0.0138 mmol) was treated with acetic anhydride (0.5 $cm^3$) in pyridine (1 $cm^3$) for 2 h at room temp. The product was chromatographed (0.5 g) with acetone–toluene (1 : 3) to give the *octa*-N,O-*acetyl derivative* **10a** (8.8 mg, 92%) as a syrup (Found: C, 51.0; H, 5.6; N, 3.8. $C_{30}H_{38}N_2O_{17}$ requires C, 51.6; H, 5.5; N, 4.0%); $[\alpha]_D^{24}$ +137 (*c* 0.44, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1740 (OAc) and 1690 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.98 (1 H, d, $J_{1',5a'}$ 5.9, 5a'-H), 5.71 (1 H, dd, $J_{2',4'}$ 7.1, $J_{3',4'}$ 7.3, 4'-H), 5.68 (1 H, dd, $J_{2',3'}$ 9.8, $J_{3',4'}$ 7.3, 3'-H), 5.51 (1 H, d, $J_{7,8}$ 8.8, 7-H), 5.47 (1 H, dd, $J_{1,8}$ 2.6, $J_{7,8}$ 8.8, 8-H), 5.06 (1 H, ddd, $J_{1',2'}$ 4.0, $J_{2',3'}$ 9.8, $J_{2',4'}$ 7.1, 2'-H), 4.86 (1 H, d, $J_{1,5}$ 9.5, 5-H), 4.81 (1 H, dd, $J_{1,5}$ 9.5, $J_{1,8}$ 2.6, 1-H), 4.68 and 4.32 (each 1 H, ABq, $J_{gem}$ 13.0, 6'-$H_2$), 4.49 (1 H, dd, $J_{1',2'}$ 4.0, $J_{1',5a'}$ 5.9, 1'-H), 4.25 and 3.89 (each 1 H, ABq, $J_{gem}$ 12.1, 6-C$H_2$OAc), 3.73 (1 H, s, OH) and 2.63, 2.12, 2.09, 2.063, 2.057, 2.04, 2.03 and 2.01 (each 3 H, 8 s, 8 × Ac).

***N*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)-cyclopentyl]-*N'*-[2',3',6'-tri-*O*-benzyl-4'-*O*-(2'',3'',4'',6''-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranosyl]-thiourea 42**

Trehazolamine **2** (58.1 mg, 0.324 mmol) was allowed to couple with the isothiocyanate **31α** (410 mg, 0.404 mmol, 1.25 mol equiv.) in 75% aq. THF (10 $cm^3$) for 18 h at room temp. The product was chromatographed on a column of silica gel (50 g) with EtOAc–hexane (1 : 3, v/v) ⟶ EtOH–PhMe (1 : 10, v/v) as eluent to afford the *thiourea* **42** (335 mg, 86.7%) as a hygroscopic syrup (Found: C, 67.9; H, 6.8; N, 2.3. $C_{68}H_{76}N_2O_{15}S{\cdot}0.5H_2O$ requires C, 67.9; H, 6.45; N, 2.3%); $[\alpha]_D^{25}$ +120 (*c* 2.80, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3320 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.65 (1 H, d, *J* 7.0, NH or N'H), 7.31–7.10 (35 H, m, 7 × Ph), 6.79 (1 H, br s, N'H or NH), 5.57 (1 H, d, *J* 3.7, 1- or 1'-H), 5.13 (1 H, br s, 1'- or 1-H) and 4.89–2.87 (37 H, m).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-[2',3',6'-tri-*O*-benzyl-4'-*O*-(2'',3'',4'',6''-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranosylamino]-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 50**

The thiourea **42** (335 mg, 0.281 mmol) was treated with six portions of yellow HgO (each 183 mg, 0.843 mmol, 3 mol equiv.; total 1.91 g, 5.06 mmol, 18 mol equiv.), as in the preparation of compound **45**, to give the *isourea* **50** (308 mg, 94.6%) as a hygroscopic syrup (Found: C, 69.4; H, 6.3; N, 2.4. $C_{68}H_{74}N_2O_{15}{\cdot}H_2O$ requires C, 69.4; H, 6.5; N, 2.4%); $[\alpha]_D^{23}$ +72 (*c* 1.0, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3420 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 7.30–7.05 (35 H, m, 7 × Ph), 5.49 (1 H, d, *J* 3.7, 1- or 1'-H), 5.36 (1 H, d, *J* 5.1, 1'- or 1-H), 4.86–4.34 (15 H, m, 1''-H and 7 × PhC$H_2$), 4.46 (1 H, s, OH), 4.28 (1 H, d, $J_{1,5}$ 8.1, 5-H), 4.26 (1 H, s, OH), 3.88–3.38 (18 H, m) and 3.47 (1 H, dd, *J* 3.7 and 9.9, 2'- or 2''-H).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-3-[4'-*O*-(α-D-Glucopyranosyl)-α-D-glucopyranosylamino]-6-hydroxymethyl-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol [4'-*O*-(α-D-glucopyranosyl)-trehazolin] 11**

O-Debenzylation of the isourea **50** (308 mg, 0.266 mmol) gave, as in the preparation of compound **7**, the trehazolin analogue **11** (114 mg, 81.3%) as a powder; $[\alpha]_D^{26}$ +185 (*c* 1.55, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3420 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$), 5.26 (1 H, d, *J* 3.3, 1'- or 1''-H), 5.19 (1 H, d, *J* 5.1, 1''- or 1'-H), 4.78 (1 H, dd, $J_{1,5}$ 8.4, $J_{1,8}$ 1.9, 1-H), 4.20 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.05 (1 H, dd, $J_{1,8}$ 1.9, $J_{7,8}$ 4.8, 8-H), 3.80 (1 H, d, $J_{7,8}$ 4.8, 7-H), 3.75–3.27 (13 H, m) and 3.43 (1 H, dd, *J* 3.3 and 9.7, 2'- or 2''-H).

**(1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-[2',3',6'-tri-*O*-acetyl-4'-*O*-(2'',3'',4'',6''-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranosylimino]-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 11a**

The free base **11** (88.0 mg, 0.167 mmol) was acetylated conventionally to give, after purification on a column of silica gel (12 g) with acetone–PhMe (1 : 4, v/v), the *undeca*-N,O-*acetyl derivative* **11a** (155 mg, 93.5%) as a syrup (Found: C, 49.7; H, 5.6; N, 2.7. $C_{41}H_{54}N_2O_{26}$ requires C, 49.7; H, 5.5; N, 2.8%); $[\alpha]_D^{23}$ +145 (*c* 2.78, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1745 (OAc) and 1695 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.54 (1 H, d, $J_{7,8}$ 8.8, 7-H), 5.50 (1 H, d, *J* 4.4, 1'- or 1''-H), 5.45 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.8, 8-H), 5.44 (1 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.1, 3'-H), 5.41 (1 H, d, *J* 4.0, 1''- or 1'-H), 5.38 (1 H, dd, $J_{2'',3''}$ 10.3, $J_{3'',4''}$ 10.2, 3''-H), 5.06 (1 H, dd, $J_{3'',4''}$ 10.2, $J_{4'',5''}$ 10.4, 4''-H), 4.93 (1 H, dd, *J* 4.4 and 10.3, 2'- or 2''-H), 4.89 (1 H, d, $J_{1,5}$ 9.9, 5-H), 4.86 (1 H, dd, *J* 4.0 and 10.3, 2''- or 2'-H), 4.77 (1 H, dd, $J_{1,5}$ 9.9, $J_{1,8}$ 3.3, 1-H), 4.46 (1 H, dd, $J_{5',6'}$ 2.2, $J_{gem}$ 12.1, 6'-H), 4.27 (1 H, dd, $J_{5'',6''}$ 3.7, $J_{gem}$ 12.5, 6''-H), 4.25 (1 H, m, 5'- or 5''-H), 4.17 and 3.91 (each 1 H, ABq, $J_{gem}$ 11.9, C$H_2$OH), 4.16 (1 H, dd, $J_{5',6'}$ 4.0, $J_{gem}$ 12.1, 6'-H), 4.06 (1 H, dd, $J_{5'',6''}$ 2.6, $J_{gem}$ 12.5, 6''-H), 3.97 (1 H, dd, $J_{3',4'}$ 9.1, $J_{4',5'}$ 9.2, 4'-H), 3.96 (1 H, m, 5''- or 5'-H), 3.76 (1 H, s, OH) and 2.70, 2.14, 2.103, 2.101, 2.098, 2.09, 2.03, 2.01, 2.00, 1.99 and 1.95 (each 3 H, 11 s, 11 × Ac).

***N*-[(1*R*)-(1,3,5/2,4)-2,3,4,5-Tetrahydroxy-2-(hydroxymethyl)-cyclopentyl]-*N'*-[2',3',6'-tri-*O*-benzyl-4'-*O*-(2'',3'',4'',6''-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranosyl]-thiourea 43**

Trehazolamine **2** (35.9 mg, 0.200 mmol) was allowed to react

with the isothiocyanate **33α** (250 mg, 0.247 mmol, 1.24 mol equiv.) in 75% aq. THF (8 $cm^3$) for 28 h at room temp. The product was chromatographed on a column of silica gel (34 g) with EtOAc–hexane (1 : 5, v/v) ⟶ EtOH–PhMe (1 : 18, v/v) as eluent to give the *thiourea* **43** (140 mg, 58.7%) as a hygroscopic syrup (Found: C, 68.0; H, 6.8; N, 2.3. $C_{68}H_{76}N_2O_{15}S{\cdot}0.5H_2O$ requires C, 67.9; H, 6.45; N, 2.3%); $[\alpha]_D^{25}$ +78 (*c* 3.0, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3330 (OH and NH) and 1540 (NH); $\delta_H$(270 MHz; $CDCl_3$) 7.68 (1 H, d, *J* 6.2, NH or N'H), 7.36–7.12 (35 H, m, 7 × Ph), 6.77 (1 H, br s, N'H or NH), 5.12 (1 H, br s, 1'-H) and 5.03–3.25 (38 H, m).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Hydroxymethyl-3-[2',3',6'-tri-*O*-benzyl-4'-*O*-(2'',3'',4'',6''-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranosylamino]-2-oxa-4-azabicyclo[3.3.0]oct-3-ene-6,7,8-triol 51

The thiourea **43** (253 mg, 0.212 mmol) was treated with five portions of yellow HgO (each 138 mg, 0.636 mmol, 3 mol equiv.; total 690 mg, 1.06 mmol, 15 mol equiv.), as in the preparation of compound **45**, to give the *isourea* **51** (243 mg, 100%) as a hygroscopic syrup (Found: C, 69.4; H, 6.3; N, 2.4. $C_{68}H_{74}N_2O_{15}{\cdot}H_2O$ requires C, 69.4; H, 6.5; N, 2.4%); $[\alpha]_D^{26}$ +40 (*c* 1.3, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3360 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $CDCl_3$) 7.40–7.12 (35 H, m, 7 × Ph), 5.29 (1 H, br s, 1'-H), 5.01–4.26 (17 H, m) and 3.93–3.32 (21 H, m).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-3-[4'-*O*-(β-D-Glucopyranosyl)-α-D-glucopyranosylamino]-6-hydroxymethyl-2-oxa-4-azabicyclo-[3.3.0]oct-3-ene-6,7,8-triol [4'-*O*-(β-D-glucopyranosyl)-trehazolin] 12

O-Debenzylation of the isourea **51** (50.0 mg, 0.0430 mmol) was carried out, as in the preparation of compound **7**, to give the trehazolin analogue **12** (20.9 mg, 92.0%) as a powder; $[\alpha]_D^{25}$ +94 (*c* 0.90, water); $\nu_{max}$(KBr)/$cm^{-1}$ 3410 (OH and NH) and 1660 (C=N); $\delta_H$(270 MHz; $D_2O$) 5.19 (1 H, d, $J_{1',2'}$ 4.4, 1'-H), 4.81 (1 H, dd, $J_{1,5}$ 8.4, $J_{1,8}$ 2.2, 1-H), 4.36 (1 H, d, $J_{1'',2''}$ 7.7, 1''-H), 4.22 (1 H, d, $J_{1,5}$ 8.4, 5-H), 4.07 (1 H, dd, $J_{1,8}$ 2.2, $J_{7,8}$ 4.8, 8-H), 3.81 (1 H, d, $J_{7,8}$ 4.8, 7-H), 3.75–3.23 (13 H, m) and 3.17 (1 H, dd, $J_{1'',2''}$ 7.7, $J_{2'',3''}$ 9.2, 2''-H).

### (1*S*,5*R*,6*R*,7*S*,8*S*)-6-Acetoxymethyl-4-*N*,7-*O*,8-*O*-triacetyl-3-[2',3',6'-tri-*O*-acetyl-4'-*O*-(2'',3'',4''6''-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosylimino]-2-oxa-4-azabicyclo[3.3.0]octane-6,7,8-triol 12a

Conventional acetylation of the free base **12** (13.3 mg, 0.025 mmol) gave, after chromatography on a column of silica gel (1 g) with acetone–PhMe (1 : 3, v/v) as eluent, the *undeca*-N,O-*acetyl derivative* **12a** (22.5 mg, 90.8%) as a syrup (Found: C, 49.7; H, 5.6; N, 2.7. $C_{41}H_{54}N_2O_{26}$ requires C, 49.7; H, 5.5; N, 2.8%); $[\alpha]_D^{23}$ +54 (*c* 0.41, $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3480 (OH), 1745 (OAc) and 1695 (NAc and C=N); $\delta_H$(270 MHz; $CDCl_3$) 5.54 (1 H, d, $J_{7,8}$ 8.8, 7-H), 5.51 (1 H, d, $J_{1',2'}$ 4.4, 1'-H), 5.45 (1 H, dd, $J_{1,8}$ 3.3, $J_{7,8}$ 8.8, 8-H), 5.34 (1 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.5, 3'-H), 5.15 (1 H, dd, $J_{2'',3''}$ 9.0, $J_{3'',4''}$ 9.5, 3''-H), 5.07 (1 H, dd, $J_{3'',4''}$ 9.5, $J_{4'',5''}$ 10.4, 4''-H), 4.98 (1 H, dd, $J_{1',2'}$ 4.4, $J_{2',3'}$ 10.3, 2'-H), 4.94 (1 H, dd, $J_{1'',2''}$ 8.1, $J_{2'',3''}$ 9.0, 2''-H), 4.88 (1 H, d, $J_{1,5}$ 9.9, 5-H), 4.76 (1 H, dd, $J_{1,5}$ 9.9, $J_{1,8}$ 3.3, 1-H), 4.51 (1 H, d, $J_{1'',2''}$ 8.1, 1''-H), 4.47 and 4.04 (each 1 H, 2 dd, *J* 2.2 and 1.4, $J_{gem}$ 12.5, 6'- or 6''-$H_2$), 4.38 and 4.14 (each 1 H, 2 dd, *J* 4.2 and 2.8, $J_{gem}$ 12.5, 6''- or 6'-$H_2$), 4.16 (1 H, m, 5'- or 5''-H), 4.13 and 3.90 (each 1 H, ABq, $J_{gem}$ 11.5, C$H_2$OH), 3.77 (1 H, s, OH), 3.72 (1 H, dd, $J_{3',4'}$ 9.5, $J_{4',5'}$ 10.2, 4'-H), 3.66 (1 H, m, 5''- or 5'-H) and 2.64, 2.14, 2.10, 2.09, 2.08, 2.07, 2.05, 2.01, 2.00, 1.99 and 1.97 (11 s, each 3 H, 11 × Ac).

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