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Effect on human liver glycosidases and short syntheses of 1*a*,2*a*,6*a*,7*a*,7a*β*-1,2,6,7-tetrahydroxypyrrolizidine from D-*glycero*-D-*gulo*-heptono-1,4-lactone

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ABSTRACT

The synthesis of 1*a*,2*a*,6*a*,7*a*,7a*β*-1,2,6,7-tetrahydroxypyrrolizidine (**1**) from D-*glycero*-D-*gulo*-heptono-1,4-lactone (**6**) by two different routes is reported. The effects of **1** on the inhibition of 15 human liver glycosidases are described.

INTRODUCTION

Several naturally occurring polyhydroxylated pyrrolidines, pyrrolizidines, and indolizidines are powerful and specific inhibitors of glycosidases[1,2]. In recent years, plagiarism of plant chemistry has led to the synthesis of powerful inhibitors of other glycosidases[3–5]. It is now clear that, although changes in stereochemistry of the hydroxyl groups have profound effect on the selectivity of glycosidase inhibition, it is not easy to predict the effects of such changes[6]. For example, 6-epicastanospermine (**2**) is a glucosidase inhibitor even though the stereochemistry of the four adjacent chiral centres in the piperidine is similar to those in the pyranose form of mannose[7]; also, 1,7*a*-diepialexine (**3**), structurally similar to the powerful mannosidase inhibitor swainsonine (**4**), is an inhibitor of fungal glucan (1→4)-*a*-D-glucosidase[8]. Also, *β*-*C*-methyldeoxymannojirimycin[11] (**5**) is a strong and specific *a*-L-fucosidase inhibitor, but has no effect on human liver mannosidases[9].

With a few exceptions[10], sugars have been the starting materials used in the synthesis of such compounds as castanospermines (for example **2**)[11,12], alexines (for example **3**)[13], and homonojirimycins[14] (for example **5**). Invariably in the syntheses of these compounds having five adjacent chiral centres and six or seven adjacent functional groups, the strategy chosen has been to start from a hexose and to introduce the additional chiral centre late in the synthesis. An alternative is to start from derivatives of heptoses, that is, by very early introduction of the additional chiral centre. There are

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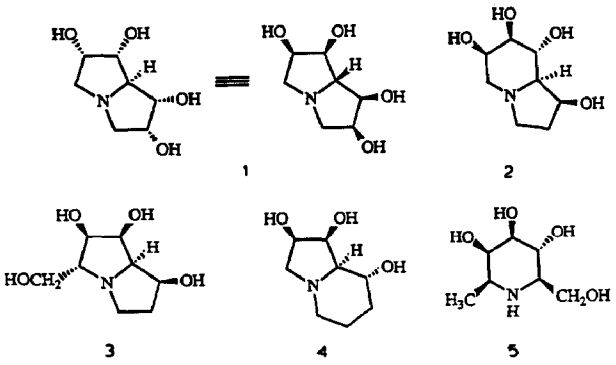
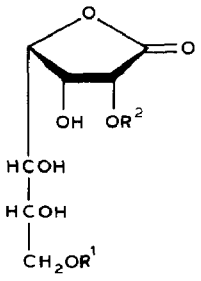


rather few studies on the protecting-group chemistry of even readily available heptonolactones[15]. Although at present there are rather few examples of syntheses from heptose derivatives (a beautiful example is described in ref. 16), it is clear that suitably protected heptonolactones are likely to be powerful and readily manipulable chiral pool materials[17]. In view of the difficulty of predicting the effect of stereochemical and alkylation changes on the ability of simple monocyclic pyrrolidines to inhibit glycosidases, and in order to demonstrate the ease of preparation of highly functionalised heterocycles from heptoses, we have prepared the *meso*-pyrrolizidine **1** from the readily available lactone **6** and have examined the effect of **1** on the activity of human liver glycosidases.

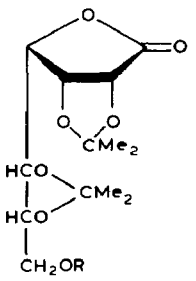
RESULTS AND DISCUSSION

Synthesis of tetrahydroxypyrrolizidine (**1**). — The synthesis of 1*a*,2*a*,6*a*,7*a*,7a*β*-1,2,6,7-tetrahydroxypyrrolizidine (**1**), having five adjacent chiral centres and seven adjacent carbon atoms bearing functional groups, requires the joining of C-1, C-4, and C-7 of the heptonolactone **6** by nitrogen with inversion of configuration at C-4. The order in which the formation of the different carbon–nitrogen bonds are formed is variable, although protection of the hydroxyl groups at C-2, C-3, C-5, and C-6, is required; di-isopropylidene protection of the hydroxyl functions is likely to assist the intramolecular cyclisations to the pyrrolidine rings, since fused five-five membered rings are formed.

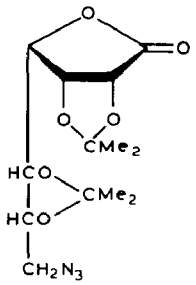
The primary hydroxyl group in **6** was protected as the *tert*-butyldiphenylsilyl ether by reaction with *tert*-butylchlorodiphenylsilane in the presence of imidazole to afford **7** in 55% yield[18]. Although the chlorosilane was present in only slight excess, a significant proportion (18%) of a disilyl derivative was also formed; this by-product was tentatively assigned as the 2,7-disilyl ether **8**, as hydroxyl groups *a* to lactone carbonyl groups show enhanced reactivity in silylation reactions[19]. Reaction with 2,2-dimethoxypropane in the presence of DL-camphorsulphonic acid as catalyst gave the diisopropylidene acetal **9** (68% yield), in which the presence of two 5-ring acetals is clearly indicated by two singlets for the quaternary isopropylidene carbons at $\delta \sim 110$ in the ^{13}C-n.m.r.



6 $R^1 = R^2 = H$
7 $R^1 = [Si]; R^2 = H$
8 $R^1 = R^2 = [Si]$



9 R = [Si]
10 R = H
11 R = SO_2CF_3



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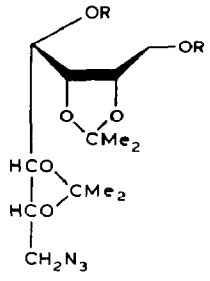
[Si] = $PhBu^tSi$



13 R = H
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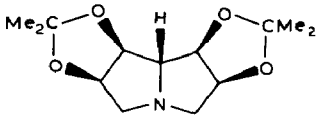

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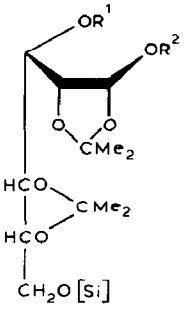
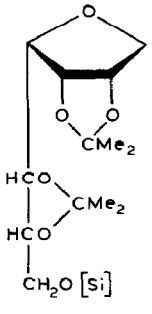


16 $R^1 = R^2 = H$
17 $R^1 = R^2 = SO_2CH_3$
18 $R^1 = H; R^2 = SO_2CH_3$



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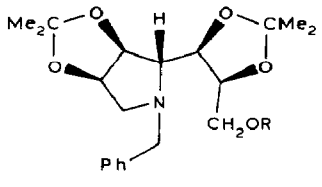
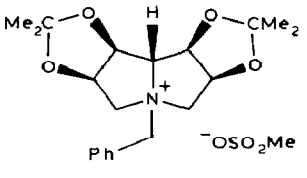


20 R = [Si]
21 R = H
22 R = SO_2CH_3



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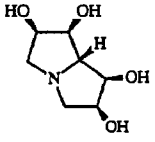
spectrum; the quaternary carbon of a six-ring acetal generally[21,22] appears below δ 100. If the acetonation reaction was stopped before completion, both 5- and 6-ring monoacetals could be isolated from the mixture, indicating that **9** is the thermodynamic product.

One approach to the synthesis of **1** from the divergent intermediate **9** requires initial introduction of nitrogen at C-7. Access was gained to C-7 by cleavage of the silyl ether with fluoride ion to give the primary alcohol **10** in 86% yield. Esterification of **10** with trifluoromethane sulphonic anhydride afforded the triflate **11** which with sodium azide in *N,N*-dimethylformamide at room temperature gave the azide **12** (77% yield from **10**). The lactone **12** was reduced by sodium borohydride in ethanol to the azidodiol **13** (93% yield), which was treated with an excess of methanesulphonyl chloride in pyridine in the presence of 4-dimethylaminopyridine to give the dimesylate **14** (94% yield). Hydrogenation of the azidodimesylate **14** in ethanol in the presence of a catalyst of palladium black, followed by heating in ethanol in the presence of sodium acetate, led directly to the tetracyclic pyrrolizidine **15** in 76% yield. In **15**, C-1 is equivalent with C-7, C-2 with C-6, and C-3 with C-5, giving only five signals in the δ 2.5–5.0 region of the ^{1}H-n.m.r. spectrum, and only four signals in the δ 55–85 region of the ^{13}C-n.m.r. spectrum; additionally in the ^{13}C-n.m.r. spectrum, the quaternary isopropylidene carbons are equivalent and there are two pairs of equivalent isopropylidene methyl carbons. Removal of the isopropylidene groups from **15** by treatment with aqueous trifluoroacetic acid gave the target tetrahydroxypyrrolizidine **1** in 90% yield (15% overall yield for the ten steps from heptonolactone **6**). It is clear that removal of the two cyclic acetals in **15** resulted in a change of the torsion angles within the structure, as there are significant changes in the coupling constants between **1** and **15**.

An alternative synthesis of **1** from the fully protected lactone **9** involves initial formation of a pyrrolidine ring between C-1 and C-4. Reduction of the lactone **9** with lithium aluminum hydride in tetrahydrofuran gave the diol **16** in 77% yield, providing access to the C-1 and C-4 hydroxyl groups while all of the other oxygen functions are protected. The silyl diol **16** was then converted into the dimesylate **17** (66% yield) by treatment with methanesulphonyl chloride in pyridine in the presence of 4-dimethylaminopyridine; the anhydro sugar **19** (32% yield) was also obtained in this reaction, presumably arising from intramolecular cyclisation of the monomesylate **18**. Nitrogen was introduced by treatment of the dimesylate **17** with benzylamine giving the monocyclic pyrrolidine **20** in 72% yield; efficient cyclisation of 1,4-dimesylates to pyrrolidines on treatment with benzylamine is a well precedented procedure[22,23]. The formation of the second pyrrolidine ring was achieved by first removing the silyl protecting group from C-7 of **20** by treatment with fluoride ion (84% yield). Subsequent mesylation of the primary alcohol **21** gave the unstable mesylate **22**, which spontaneously closed to give the *N*-benzyl pyrrolizidinium salt **23**. Cleavage of the *N*-benzyl group by hydrogenation of **23** in ethanol in the presence of palladium black, followed by neutralisation with sodium hydrogencarbonate, gave the pyrrolizidine diacetal **15** (31% yield from **21**), identical in all respects to the sample of **15** prepared by the foregoing alternative procedure.

Glycosidase inhibition. — The effect of 1α, 2α, 6α, 7α, 7aβ-1, 2, 6, 7-tetrahydroxypyrrolizidine (**1**) on the activity of 15 human liver glycosidases was investigated (for assay methods, see ref. 24). Compound **1** is a weak inhibitor of all of the human lysosomal, Golgi II, and neutral α-D-mannosidases (I_{50} approximately M) that can be

assayed with a synthetic substrate; in addition, it is also a weak inhibitor of *α*-L-fucosidase, *α*- and *β*-D-galactosidase, and the broad specificity *β*-D-galactosidase–*β*-D-glucosidase. The pyrrolizidine **1** is closely structurally related to 1,4-dideoxy-1,4-imino-L-allitol (**24**), which is also a relatively weak inhibitor of lysosomal *α*-D-mannosidase (K_i 120*μ*M). Compound **24** is comparable to the pyrrolizidine **1** in its inhibition of the neutral and Golgi II *α*-D-mannosidases[25]; both **24** and **1** have a relatively broad specifity of inhibition of glycosidases[24]. In contrast, the closely related indolizidine, 8,8a-diepiswainsonine (**25**) is a very effective and specific inhibitor of lysosomal (K_i 2*μ*M) and Golgi-processing *α*-D-mannosidase, both *in vivo* and *in vitro*. These results suggest that the indolizidine **25** fits the active site of the *α*-D-mannosidases more closely than **1** or **24**. Further studies on the comparison of stereoisomers of **1** with modified swainsonines and the corresponding open-chain analogues are in progress.



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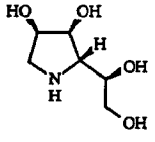

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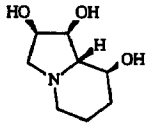

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In summary, this paper reports the easy synthesis of a tetrahydroxypyrrolizidine from a heptonolactone, indicates that simply protected heptonolactones may be powerful intermediates for the synthesis of highly functionalised targets, and suggests that the properties of polyhydroxylated bicyclic nitrogen heterocycles as glycosidase inhibitors are worthy of further investigation.

EXPERIMENTAL

General methods. — Melting points were recorded on a Kofler block and are corrected. Infrared spectra were recorded on either a Perkin–Elmer 781 spectrophotometer or a Perkin–Elmer 1750 i.r.–f.t. spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path-length of 10 cm; concentrations are given in $g \cdot 100^{-1}$ mL. ^{1}H-N.m.r. spectra were run either at 200 MHz on a Varian Gemini 200 spectrometer, or at 300 MHz on a Bruker WH 300 spectrometer. Chemical shifts are quoted on the *δ* scale using residual solvent as the internal standard. ^{13}C-N.m.r. spectra were recorded at 50 MHz on a Varian Gemini 200 spectrometer; for samples in D_2O, 1,4-dioxane (*δ* 67.2) was added as a reference. Mass spectra were recorded on either a VG Micromass ZAB 1F, a VG Mass lab 20-250 or a TRIO 1 spectrometer using chemical ionisation (c.i.) or desorption chemical ionisation (d.c.i.) techniques. Microanalyses were performed by the microanalytical service of the Dyson Perrins laboratory. T.l.c. was performed on glass plates coated with Silica Gel Blend 41 (80% Silica Gel HF_{254} and 20% Silica Gel G) or on aluminium plates coated with Merck Silica Gel $60F_{254}$. Compounds were detected with a spray of 0.2% (w/v) ceric sulphate and 5%

ammonium molybdate in 2M H_2SO_4, or 0.5% ninhydrin in MeOH (for amines). Flash chromatography was carried out with Sorbsil C60 40/60 flash silica gel. Dry-column chromatography was carried out using Merck Kieselgel 60H. Ion-exchange columns were packed with Aldrich 50X, 8–100 resin in the H^+ form. Pyridine and benzylamine were distilled (and stored) over KOH. Hexane was distilled to remove involatile fractions. Immediately prior to use, *N,N*-dimethylformamide (DMF) and CH_2Cl_2 were distilled from CaH_2, and Ocolane (THF) was distilled from sodium benzophenone ketyl. D-*glycero*-D-*gulo*-Heptono-1,4-lactone (**6**) was obtained from Sigma.

7-O-tert-*Butyldiphenylsilyl*-D-glycero-D-gulo-*heptono-1,4-lactone* (**7**) *and 2,7-di*-O-tert-*butyldiphenylsilyl*-D-glycero-D-gulo-*heptono-1,4-lactone* (**8**). — D-*glycero*-D-*gulo*-Heptono-1,4-lactone (**6**, 10 g, 48.08 mmol) and imidazole (4.98 g, 1.5 equiv) were added to dry DMF (25 mL) and the mixture was stirred at 0° under nitrogen. *tert*-Butylchlorodiphenylsilane (13.74 mL, 1.1 equiv) was added slowly, after which the mixture was allowed to warm up to room temperature during 3 h. After 22 h, t.l.c. (EtOAc) indicated that the mixture contained the desired monosilyl derivative (R_F 0.65) and a smaller amount of another carbohydrate derivative (R_F 0.9). The crude mixture was shaken with water (50 mL), causing a white precipitate to form. Ethyl acetate (90 mL) was added and the layers were separated after shaking. The aqueous layer was back-extracted with more EtOAc (25 mL). The combined organic extracts were washed with saturated aq. NaCl (4 × 25 mL) and dried ($MgSO_4$). Evaporation of the solvent followed by dry-column chromatography (2:1 hexane–EtOAc, increasing the eluant polarity with each fraction) gave compound (**7**) (11.02 g, 55%) as a white solid, m.p. 54–57° (Found: C, 61.58; H, 6.86%. $C_{23}H_{30}O_7Si$ requires: C, 61.87; H, 6.77%); $[\alpha]_D^{20}$ −10.56° (*c*, 0.99 $CHCl_3$); ν_{max} ($CDCl_3$) 3410 (broad, OH) and 1790 cm^{-1} (γ-lactone); δ_H ($CDCl_3$): 7.65–7.69 (4 H, m, ArH), 7.30–7.42 (6 H, m, ArH), 5.14 (1 H, br s, OH), 4.75 (1 H, br s, OH), 4.58 (2 H, m, H-3 and H-4), 4.49 (1 H, m, H-2), 4.06 (2 H, m, H-5 and H-6), 3.81–3.91 (2 H, m, H-7 and H-7′), 3.49 (1 H, br s, OH), 3.08 (1 H, br s, OH), and 1.08 [9 H, s, C*Me*$_3$]; δ_C ($CDCl_3$): 176.74 (s, CO), 135.66 (d, ArC), 132.95 (s, ArC), 130.09, (d, ArC), 128.00 (d, ArC), 79.36, 70.74, 71.10 and 70.65 (4 d, C-2, 3, 4, 5, and 6), 64.46 (t, C-7), 26.73 (q, C*Me*$_3$), and 19.07 (s, *C*Me$_3$); *m/z* (NH_3 c.i.) 464 (M + NH_4^+, 100%) and 447 (MH^+, 18); and compound **8** (5.94 g, 18%) as a colourless, viscous oil, $[\alpha]_D^{20}$ −4.08° (*c*, 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3440 (broad, OH) and 1790 cm^{-1} (γ-lactone); δ_H ($CDCl_3$): 7.82–7.84 (2 H, m, ArH), 7.63–7.73 (8 H, m, ArH), 7.33–7.53 (10 H, m, ArH), 4.40 (1 H, d, $J_{2,3}$ 4.8 Hz, H-2), 4.37 (1 H, dd, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 3.6 Hz, H-4), 4.18 (1 H, dd, H-3), 4.04 (1 H, dd, $J_{5,6}$ 8.4 Hz, H-5), 3.82–3.92 (2 H, m, H-7 and H-7′), 3.16 (2 H, br s, 3-OH and 6-OH), 2.71 (1 H, s, 5-OH), 1.18, 1.17, 1.13, 1.09, 1.08, 1.07, and 1.06 [18 H, 7s, C*Me*$_3$]; δ_C ($CDCl_3$): 136.13 (d, ArC), 135.70 (d, ArC), 133.02, 132.49 and 131.36 (3 s, ArC), 130.70 (d, ArC), 130.49 (s, ArC), 130.26 (d, ArC), 128.33 (d, ArC), 128.13 (d, ArC), 128.01 (d, ArC), 77.84, 71.89, 71.67, 70.75 and 70.42 (5 d, C-2,3,4,5, and 6), 64.28 (t, C-7), 26.78 and 26.61 (2q, C*Me*$_3$), 19.26 and 19.15 (2 s, *C*Me$_3$); *m/z* (NH_3 d.c.i.) 702 (M+NH_4^+, 18%).

7-O-tert-*Butyldiphenylsilyl-2,3:5,6-di*-O-*isopropylidene*-D-glycero-D-gulo-*heptono-1,4-lactone* (**9**). — Compound **7** (3.00 g, 6.73 mmol) and DL-camphorsulphonic acid

(0.15 g, 5%) were dissolved in dry acetone (60 mL). 2,2-Dimethoxypropane (3.50 g, 5 equiv) was added and the mixture was stirred for 22 h at 50° under reflux. The reaction was quenched by addition of excess $NaHCO_3$, at which stage t.l.c. (6:1 hexane–EtOAc) indicated that the mixture contained three compounds, one major product (R_F 0.6) together with two minor products (R_F 0.8 and 0.1). After filtration of the mixture and evaporation of the solvent, the residue was purified by flash chromatography (8:1 hexane–EtOAe), yielding compound **9** (2.40 g, 68%) as a white, crystalline solid, m.p. 104–106° (Found: C, 66.19; H, 7.58% $C_{29}H_{38}O_7Si$ requires: C, 66.13; H, 7.27%); $[\alpha]_D^{20}$ −21.64° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1790 (γ-lactone), 1386 and 1377 cm^{-1} (CME_2); δ_H ($CDCl_3$): 7.66–7.70 (4 H, m, ArH), 7.39–7.49 (6 H, m, ArH), 4.75–4.79 (2 H, m, H-3 and H-4), 4.64 (1 H, d, $J_{2,3}$ 5 Hz, H-2), 4.48 (1 H, dd, H-5), 4.33 (1 H, ddd, $J_{6,7}$ 6.5, $J_{6,7'}$ 3 Hz, H-6), 3.97 (1 H, dd, $J_{7,7'}$ 11 Hz, H-7), 3.70 (1 H, dd, H-7'), 1.50, 1.48, 1.40 and 1.25 (12 H, 4 s, C*Me*$_2$), and 1.11 [9 H, s, C*Me*$_3$]; δ_C ($CDCl_3$): 173.22 (s, CO), 135.66 (d, ArC), 133.03 (s, ArC), 130.26 (d, ArC), 128.08 (d, ArC), 114.44 (s, ring *C*Me$_2$), 109.12 (s, side-chain, *C*Me$_2$), 78.25, 76.44, 76.26, 75.93 and 75.79 (5 d, C-2, 3, 4, 5 and 6), 62.75 (t, C-7), 27.48, 26.68, 25.41 and 25.14 (4 q, C*Me*$_2$), 26.87 (q, C*Me*$_3$), and 19.08 (s, *C*Me$_3$); *m/z* (NH_3 c.i.) 469 (*M*H$^+$ - Me_2CO, 100%), 544 (*M* + NH_4^+, 89) and 527 (*M*H$^+$, 57).

*2,3:5,6-Di-*O*-isopropylidene-*D*-glycero-*D*-gulo-heptono-1,4-lactone* (**10**). — Compound **9** (4.11 g, 7.81 mmol) was dissolved in dry THF (200 mL) and the solution was stirred under nitrogen. Tetrabutylammonium fluoride (11.7 ml of a M solution in THF, 1.5 equiv) was added dropwise. After 1,5 h, t.l.c. (6:1 hexane–EtOAc) indicated one product at the baseline but no starting material (R_F 0.6). Evaporation of the solvent gave a pale-yellow oil that was purified by flash chromatography (3:2 EtOAc–hexane) yielding compound **10** (1.93 g, 86%) as a white, crystalline solid, m.p. 115–120° (Found: C, 54.46; H, 6.99%. $C_{13}H_{20}O_7$ requires: C, 54.16; H, 6.99%); $[\alpha]_D^{20}$ −53.4° (*c*, 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 3560 (OH), 1790 (γ-lactone), 1388 and 1379 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 5.01 (1 H, dd, $J_{2,3}$ 5.7, $J_{3,4}$ 3.9 Hz, H-3), 4.80–4.87 (2 H, m, H-2 and H-4), 4.50 (1 H, dd, $J_{4,5}$ 6.6, $J_{5,6}$ 8.6 Hz, H-5), 4.35 (1 H, ddd, $J_{6,7}$ 3.7, $J_{6,7'}$ 3.0 Hz, H-6), 3.91 (1 H, ddd, $J_{7,7'}$ 12.0, $J_{7,OH}$ 4.8 Hz, H-7), 3.77 (1 H, ddd, $J_{7',OH}$ 8.0 Hz, H-7'), 2.14 (1 H, dd, OH), 1.54, 1.50, 1.42, and 1.40 (12 H, 4 s, C*Me*$_2$); δ_C ($CDCl_3$) 173.37 (s, CO), 114.53 (s, ring *C*Me$_2$), 109.01 (s, side-chain *C*Me$_2$), 79.07, 76.40, 76.00 and 75.79 (4 d, C-2, 3, 4, 5, and 6), 60.94 (t, C-7), 27.34, 26.47, 25.52, and 24.72 (4 q, C*Me*$_2$); *m/z* (NH_3 c.i.) 189 (*M*H$^+$, 100%) and 306 (*M* + NH_4^+, 50).

*7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-*D*-glycero-*D*-gulo-heptono-1,4-lactone* (**12**). — Compound **10** (0.50 g, 1.74 mmol) was dissolved in dry CH_2Cl_2 (50 mL), dry pyridine (0.28 mL, 2 equiv) was added, and the solution was stirred at −30° under nitrogen. Trifluoromethanesulphonic anhydride (0.44 mL, 1.5 equiv) was added slowly, and after 30 min, t.l.c. (2:1 EtOAc–hexane) indicated complete conversion into product (R_F 0.9). The mixture was worked up as quickly as possible by washing with ice-cold saturated NaCl (35 mL) followed by drying over Na_2SO_4. The solvent was evaporated, leaving an orange residue which was dissolved in dry DMF (20 mL). Without further purification, NaN_3 (0.226 g, 2 equiv based on quantitative triflation) was added and the mixture stirred at room temperature under nitrogen. After 30 min, t.l.c. (2:1 hexane–

EtOAc) indicated that a product had formed (R_F 0.4). The solvent was evaporated, leaving a residue which was dissolved in CH_2Cl_2 (30 mL) and washed with water (3 × 15 mL). After drying ($MgSO_4$) and evaporation of the solvent, flash chromatography (2:1 hexane–EtOAc) yielded compound **12** (0.42 g, 77% over two steps) as a white, crystalline solid, m.p. 89–91° (Found: C, 50.10; H, 6.29; N, 13.18%. $C_{13}H_{19}N_3O_6$ requires: C, 49.84; H, 6.11; N, 13.41%); $[\alpha]_D^{20}$ +34.6° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2110 (N_3), 1795 (γ-lactone), 1386 and 1378 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 4.85–4.90 (2 H, m, H-2 and H-3), 4.77 (1 H, dd, $J_{3,4}$ 3.4, $J_{4,5}$ 8.4 Hz, H-4), 4.44–4.51 (2 H, m, H-5 and H-6), 3.57 (1 H, dd, $J_{6,7}$ 4.3, $J_{7,7'}$ 13 Hz, H-7), 3.36 (1 H, dd, $J_{6,7'}$ 3.5 Hz, H-7'), 1.58, 1.50, 1.42, and 1.40 (12 H, 4 s, C*Me*$_2$); δ_C ($CDCl_3$): 172.82 (CO), 114.86 (ring *C*Me$_2$), 109.70 (side-chain *C*Me$_2$), 78.58, 75.89, 75.53, and 75.28 (C-2, 3, 4, 5, and 6), 50.94 (C-7), 27.23, 26.40, 25.49, and 24.68 (C*Me*$_2$); *m/z* (NH_3 c.i.) 286 (*M*H$^+$ - N_2, 100%), and 331 (M + NH_4^+, 48).

*7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-*D-glycero-D-gulo-*heptitol* (**13**). — Compound **12** (1.84 g, 5.88 mmol) was dissolved in EtOH (100 mL) and stirred at 0° under N_2. Sodium borohydride (0.445 g, 2 equiv) was added and the mixture allowed to warm up to room temperature. After 18 h, t.l.c. (2:1 hexane–EtOAc) indicated that all starting material had been converted into product (R_F 0.2). The reaction was quenched by addition of an excess of solid NH_4Cl, with effervescence. Filtration and evaporation of the solvent gave a residue which was purified by flash chromatography (2:1 hexane–EtOAc) yielding compound **13** (1.74 g, 93%) as a colourless, viscous oil (Found: C, 49.26; H, 7.30; N, 13.26%. $C_{13}H_{23}N_3O_6$ requires: C, 49.20; H, 7.30; N, 13.24%); $[\alpha]_D^{20}$ +2.87° (*c* 0.94, $CHCl_3$); ν_{max} 3553 (broad, OH), 2107 (N_3), 1384 and 1375 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 4.17–4.33 (4 H, m, H-1, 1'-, 2, and 3), 3.92 (1 H, ddd, $J_{3,4}$ 4, $J_{4,5}$ 4, $J_{4,OH}$ 7 Hz, H-4), 3.80 (2 H, m, H-5 and H-6), 3.64 (1 H, dd, $J_{6,7}$ 6.8 Hz, $J_{7,7'}$ 12.7 Hz, H-7), 3.44 (1 H, dd, $J_{6,7'}$ 4.9 Hz, H-7'), 2.81 (1 H, d, 4-OH), 2.45 (1 H, br s, 1-OH), 1.53, 1.52, and 1.40 (12 H, 3 s, C*Me*$_2$); δ_C ($CDCl_3$): 109.50 and 108.94 (*C*Me$_2$), 77.34, 76.37, 75.80 and 66.53 (C-2, 3, 4, 5 and 6), 61.01 (C-1), 51.17 (C-7), 27.23, 27.16, and 25.00 (C*Me*$_2$); *m/z* (NH_3 c.i.) 290 (*M*H$^+$ - N_2, 100%).

*7-Azido-7-deoxy-2,3:5,6-di-*O*-isopropylidene-1,4-di-*O*-methylsulphonyl-*D-glycero-D-gulo-*heptitol* (**14**). — Compound **13**, (0.95 g, 3.00 mmol) and 4-dimethylaminopyridine (1 mg) were dissolved in dry pyridine (15 mL) and stirred at 0° under N_2. Methanesulphonyl chloride (1.39 ml, 6 equiv) was added slowly and after 4 h the mixture was allowed to warm up to room temperature. After 18 h, t.l.c. (2:1 hexane–EtOAc) indicated that no starting material remained (R_F 0.2) while a major product had formed (R_F 0.25). The solvent was evaporated, leaving a red oil which was dissolved in EtOAc (150 mL) and washed with water (75 mL). After drying ($MgSO_4$) the crude mixture was purified by flash chromatography (2:1 hexane–EtOAc) yielding compound **14** (1.33 g, 94%) as a colourless, viscous oil, $[\alpha]_D^{20}$ +8.22° (*c*, 1.07, $CHCl_3$); ν_{max} ($CHCl_3$) 2109 cm^{-1} (N_3); δ_H ($CDCl_3$): 4.99 (1 H, t, H-4), 4.30–4.52 (6 H, m, H-1', 2, 3, 5, and 6), 3.63 (1 H, dd, $J_{6,7}$ 6.3 Hz, $J_{7,7'}$ 13.0 Hz, H-7), 3.52 (1 H, dd, $J_{6,7'}$ 5.6 Hz, H-7'), 3.20 and 3.10 (6 H, 2 s, CH_3SO_2), 1.54, 1.53, and 1.48 (12 H, 3 s, C*Me*$_2$); δ_C ($CDCl_3$): 110.29, and 109.96 (2 s, *C*Me$_2$), 76.51, 75.53, 75.31, and 74.44 (4 d, C-2, 3, 4, 5 and 6), 67.12 (t, C-1), 50.16 (t, C-7), 39.46 and 37.28 (2 q, *C*H$_3$SO$_2$), 27.08, 26.86, and 25.20 (3 q, C*Me*$_2$); *m/z* (NH_3 i.c.) 446 (M*H*$^+$ - N_2, 100%) and 491 (*M* + NH_4^+, 95).

1a, 2a, 6a, 7a, 7aβ-1,2:6,7-Di-O-isopropylidene-1,2,6,7-tetrahydroxypyrrolizidine (**15**). — Compound **14** (0.64 g, 1.35 mmol) was dissolved in EtOH (50 mL) and palladium black (10%) was added. After degassing the solution, the mixture was stirred vigorously under hydrogen for 2 h at room temperature. At this stage, t.l.c. (2:1 hexane–EtOAc) indicated that all starting material (R_F 0.25) had reacted to give a product that remained at the baseline. The mixture was filtered through Celite to remove the catalyst, NaOAc (0.33 g, 3 equiv based on quantitative reduction) added, and the mixture stirred at 50° under nitrogen. After 12 h, t.l.c. (9:1 EtOAc–MeOH) showed that the mixture was predominantly one compound (R_F 0.5). After evaporating the solvent, the crude mixture was purified by flash chromatography (EtOAc, increasing polarity to 9:1 EtOAc–MeOH) giving compound **15** (0.26 g, 76% over two steps) as a pale-brown solid, m.p. 66–69° (Et_2O) (Found: C, 60.81; H, 8.44; N, 5.23%. $C_{13}H_{21}NO_4$ requires: C, 61.16; H, 8.29; N, 5.49%); $[a]_D^{20}$ +1.06° (*c*, 1.14, $CHCl_3$): δ_H ($CDCl_3$): 4.81 (2 H, ddd, $J_{1,2}$ 6.5, $J_{2,3}$ 5.5, $J_{2,3}$ 2.7 Hz, H-2 and H-6), 4.62 (2 H, dd, $J_{1,7a}$ 3.6 Hz, H-1 and H-7), 3.44 (1 H, t, H-7a), 3.20 (2 H, dd, $J_{3,3}$ 12.5 Hz, H-3 and H-5), 2.88 (2 H, dd, H-3 and H-5), 1.54, and 1.33 (12 H, 2 s, C*Me*$_2$); δ_C ($CDCl_3$): 113.09 (*C*Me$_2$), 82.88 and 80.22 (C-1, 2, 6, and 7), 76.18 (C-7_a), 58.71 (C-3 and C-5), 26.58, and 24.65 (C*Me*$_2$); *m/z* (NH_3 c.i.) 256 (*M*H$^+$, 100%).

1a, 2a, 6a, 7a, 7aβ-1,2,6,7-Tetrahydroxypyrrolizidine (**1**). — Compound **15** (112 mg, 0.44 mmol) was dissolved in 50% aq CF_3CO_2H (20 mL) and stirred for 6 h at room temperature. After evaporation of the solvent, the residue was dissolved in water and purified on an ion-exchange column (H^+ form), eluting with 0.5M aq. ammonia. Freeze drying afforded compound **15** (69 mg, 90%), m.p. 170–175° (dec.) (Found: C, 47.99; H, 7.48; N, 7.77%. $C_7H_{13}NO_4$ requires: C, 47.99; H, 7.48; N, 8.00%); $[a]_D^{20}$ 0° (*c*, 1.06, H_2O); ν_{max}^{KBr} 3400 cm^{-1} (very broad, OH); δ_H (D_2O): 4.14 (2 H, ddd, $J_{1,2}$ 4.3, $J_{2,3}$ 4.5, $J_{2,3a}$ 4.5 Hz, H-2 and H-6), 3.98 (2 H, dd, $J_{1,7a}$ 5.6 Hz, H-1 and H-7), 3.49 (1 H, t, H-7a), 3.06 (2 H, dd, $J_{3,3a}$ 12.1 Hz, H-3*a* and H-5*a*), and 2.79 (2 H, dd, H-3 and H-5), δ_C (D_2O): 75.22 and 72.15 (C-1, C-2, C-6, and C-7), 72.44 (C-7a), and 58.05 (C-3 and C-5); *m/z* (NH_3 d.c.i.) 176 (MH$^+$, 100%).

7-O-tert-*Butyldiphenylsilyl-2,3:5,6-di-O-isopropylidene*-D-glycero-D-gulo-*heptitol* (**16**). — 7-*O-tert*-Butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**9**, 116 mg, 0.22 mmol) was dissolved in dry THF (10 mL) and stirred at 0° under N_2. Lithium aluminium hydride (25 mg, 3 equiv) was added and the mixture allowed to warm up slowly, to room temperature. After 9 h, t.l.c. (2:1 hexane–EtOAc) indicated that no starting material remained (R_F 0.9) while a major product had formed (R_F 0.1). The reaction was quenched by the addition of excess solid NH_4Cl, the mixture filtered, and the solvent evaporated. Purification by flash chromatography (3:1 hexane–EtOAc) yielded compound **16**, (78 mg, 77%) as a colourless, viscous oil, $[a]_D^{20}$ −2.4° (*c* 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 3561 (broad, OH), 1383 and 1374 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 7.64–7.68 (4 H, m, ArH), 7.38–7.51 (6 H, m, ArH), 3.66–4.34 (9 H, 3 m, H-1, 1′, 2, 3, 4, 5, 6, 7, and 7′), 2.95 (1 H, d, $J_{4,OH}$ 6.4 Hz, 4-OH), 2.65 (1 H, t, 1-OH), 1.54, 1.44 and 1.38 (12 H, 3 s, CMe_2), and 1.09, [9 H, s, C(C*H*$_3$)$_3$]; δ_C ($CDCl_3$): 135.65 (d, ArC), 133.15

and 132.96 (2 s, ArC), 130.11 (d, ArC), 128.00 (d, ArC), 108.69 (s, CMe_2), 77.73, 77.23, 77.13 and 77.02 (4 d, C-2, 3, 5 and 6), 66.62 (d, C-4), 62.79 and 61.15 (2 t, C-1 and C-7), 27.23, 27.08, 25.11, and 25.01 (4 q, CMe_2), 26.80 (q, CMe_3), and 19.04 (s, CMe_3); *m/z* (NH_3 d.c.i.) 317 ($M-SiPh_2Bu^t + NH_4^+$, 100%), 531 (MH^+, 14).

*7-*O*-tert-Butyldiphenylsilyl-2,3:5,6-di-*O*-isopropylidene-1,4-di-*O*-methylsulphonyl-*D*-glycero-*D*-gulo-heptitol* (**17**) *and 1,4-anhydro-7-*O*-tert-butyldiphenylsilyl-1-deoxy-2,3:5,6-di-*O*-isopropylidene-*D*-glycero-*D*-gulo-heptitol* (**19**). — Compound **16** (260 mg, 0.49 mmol) and 4-dimethylaminopyridine (1 mg) were dissolved in dry pyridine (10 mL) and stirred at 0° under N_2. Methanesulphonyl chloride (0.15 mL, 4 equiv) was added slowly and after 3 h the mixture was allowed to warm up to room temperature. After 20 h, t.l.c. (3:2 hexane–EtOAc) indicated that two products had formed (R_F 0.5 and 0.8) while no starting material (R_F 0.4) remained. After evaporation of the solvent, the residue was shaken with EtOAc (60 mL), leaving an insoluble brown solid. The filtrate was washed with water (70 ml) and dried ($MgSO_4$). After filtration and evaporation of the solvent, flash chromatography (3:1 hexane–EtOAc) yielded compound **17**, (224 mg, 67%) as a colourless, viscous oil, $[\alpha]_D^{20}$ −9.40° (*c* 1.08, $CHCl_3$); δ_H ($CDCl_3$): 7.64–7.68 (4 H, m, ArH), 7.40–7.46 (6 H, m, ArH), 5.07 (1 H, dd, *J* 2.0 Hz, 7.9 Hz, H-4), 4.51–4.64 (3 H, m, H-1,1′ and 2), 4.11–4.31 (3 H, m, H-3, 5, and 6), 3.96 (1 H, dd, $J_{6,7}$ 8.2, $J_{7,7'}$ 11.0 Hz, H-7), 3.75 (1 H, dd, $J_{6,7'}$ 3.7 Hz, H-7′), 3.18 and 2.98 (6 H, 2 s, CH_3SO_2), 1.54, 1.41, 1.36, and 1.32 (12 H, 4 s, CMe_2), and 1.11 [9 H, 2, CMe_3]; δ_C ($CDCl_3$): 135.61 (d, ArC), 132.89 and 132.82 (2 s, ArC), 130.25 (d, ArC), 128.16 (d, ArC), 110.01 and 108.90 (2 s, CMe_2), 77.49, 77.05, 76.47, 75.15 and 74.72 (5 d, C-2, 3, 4, 5, and 6), 68.50 and 62.64 (2 t, C-1 and C-7), 39.53 and 36.94 (2 q, CH_3SO_2), 27.57, 26.69, 25.42, and 25.04 (4 q, CMe_2), 26.90 (q, CMe_3), 19.08 (s, CMe_3); *m/z* (NH_3 d.c.i.) 704 ($M + NH_4^+$, 100%); and compound **19** (81 mg, 32%) as a colourless, viscous oil, $[\alpha]_D^{20}$ +34.7° (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 1382 and 1375 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 7.68–7.71 (4 H, m, ArH), 7.36–7.47 (6 H, m, ArH), 4.72 (1 H, dd, $J_{2,3}$ 6.2, $J_{3,4}$ 3.5 Hz, H-3), 4.64 (1 H, dd, $J_{1',2}$ 3.5 hz, H-2), 4.50 (1 H, dd, $J_{4,5}$ 8.8, $J_{5,6}$ 5.7 Hz, H-5), 4.35 (1 H, ddd, $J_{6,7}$ 6.9, $J_{6,7'}$ 3.5 Hz, H-6), 4.10 (1 H, d, $J_{1,1'}$ 10.8 Hz, H-1), 3.90 (1 H, dd, $J_{7,7'}$ 11.0 Hz, H-7), 3.74 (1 H, dd, H-4), 3.65 (1 H, dd, H-7′), 3.50 (1 H, dd, H-1′), 1.50, 1.45, 1.41 and 1.24 (12 H, 4 s, CMe_2), and 1.10 [9 H, s, $C(CH_3)_3$]; δ_C ($CDCl_3$): 135.76 (d, ArC), 133.20 (s, ArC), 130.04 (d, ArC), 127.95 (d, ArC), 112.37 (s, ring CMe_2), 108.50 (s, side chain CMe_2), 81.31, 80.78, 80.37, 76.37 and 76.48 (5 d, C-2, 3, 4, 5, and 6), 72.82 (t, C-1), 63.15 (t, C-7), 27.81, 25.79, 25.37, and 24.36 (4 q, CMe_2), 26.84 (q, CMe_3) and 19.08 (s, CMe_3); *m/z* (NH_3 d.c.i.) 455 (M^+ - Me_2CO, 100%) and 513 (MH^+, 21).

*N-Benzyl-7-*O*-tert-butyldiphenylsilyl-1,4-dideoxy-2,3:5,6-di-*O*-isopropylidene-1,4-imino-*D*-glycero-*D*-allo-heptitol* (**20**). — Compound **17** (147 mg, 0.21 mmol) was dissolved in benzylamine (10 mL) and stirred for 72 h at 50° under nitrogen. At this stage, t.l.c. (3:1 hexane–EtOAc) indicated that no starting material remained (R_F 0.2) while a major product had formed (R_F 0.8). The benzylamine was evaporated, leaving a dark-red oil that was dissolved in EtOAc (20 mL). Silica gel was added and the solvent evaporated to pre-adsorb the compound. Flash chromatography (eluant hexane, increasing polarity to 6:1 hexane–EtOAc) yielded compound **20**, (94 mg, 72%) as a pale-yellow, viscous oil, $[\alpha]_D^{20}$ −14.08° (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 1383 and 1375 cm^{-1}

(CMe_2); δ_H ($CDCl_3$): 7.68–7.74 (4 H, m, ArH), 7.22–7.43 (11 H, m, ArH), 4.77 (1 H, d, $J_{2,3}$ 6.3 Hz, H-3), 4.65 (1 H, ddd, $J_{1,2}$ 5.0, $J_{1',2}$ 2.6 Hz, H-2), 4.38 (1 H, ddd, $J_{5,6}$ 6.9, $J_{6,7}$ 5.7, $J_{6,7'}$ 6.4 Hz, H-6), 4.23 (1 H, dd, $J_{4,5}$ 4.4 Hz, H-5), 4.06 (1 H, dd, $J_{7,7'}$ 10.8 Hz, H-7), 3.96 (1 H, d, $J_{8,8'}$ 13.5 Hz, H-8), 3.85 (1 H, dd, H-7'), 3.84 (1 H, d, H-8'), 3.42 (1 H, d, H-4), 3.02 (1 H, dd, $J_{1,1'}$ 11.7 Hz, H-1), 2.78 (1 H, dd, H-1'), 1.56, 1.48, 1.37, and 1.29 (12 H, 4 s, C*Me*$_2$), and 1.07 (9 H, s, C*Me*$_3$); δ_C ($CDCl_3$): 139.48 (s, ArC), 135.84 (d, ArC), 133.63 and 133.47 (2 s, ArC), 129.74, 128.74, 128.37, 127.72 and 126.99 (5d, ArC), 111.56 (s, ring *C*Me$_2$), 108.21 (s, side-chain *C*Me$_2$), 82.92, 80.80, 77.81, 75.35 and 68.36 (5d, C-2, 3, 4, 5, and 6), 62.69, 58.61 and 57.40 (3t, C-1,7 and 8), 26.93, 24.50, and 24.38 (3q, C*Me*$_2$), 26.70 (q, C*Me*$_3$), 19.04 (s. *C*Me$_3$); *m/z* (NH_3 d.c.i.) 232 ($PhCH_2N^+CH_2CH(OCMe_2)CH(O)CH$, 100%), 91 ($C_7H_7^+$, 33) and 602 (*M*H$^+$, 30).

N-*Benzyl-1,4-dideoxy-2,3:5,6-di*-O-*isopropylidene-1,4-imino*-D-glycero-D-allo-*heptitol* (**21**). — Compound **20** (94 mg, 0.16 mmol) was dissolved in dry THF (10 ml) and stirred at room temperature under N_2. Tetrabutylammonium fluoride (0.23 mL of a M solution in THF, 1.5 equiv) was added. After 3 h, t.l.c. (3:1 hexane–EtOAc) indicated that no starting material (R_F 0.8) remained while a major product (R_F 0.25) had formed. Evaporation of the solvent followed by flash chromatography (3:1 hexane–EtOAc) yielded compound **21** (48 mg, 84%) as a colourless, viscous oil, $[\alpha]_D^{20}$ −58.4° (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3670 (OH), 1386 and 1377 cm^{-1} (CMe_2); δ_H ($CDCl_3$): 7.29–7.39 (5 H, m, ArH), 5.68 (1 H, br s, OH), 5.00 (1 H, d, $J_{2,3}$ 6.2 Hz, H-3), 4.76 (1 H, dd, $J_{1',2}$ 4.5 Hz, H-2), 4.42 (1 H, ddd, $J_{5,6}$ 5.6, $J_{6,7}$ 5.4, $J_{6,7'}$ 10.1 Hz, H-6), 4.30 (1 H, d, $J_{8,8'}$ 12.1 Hz, H-8), 4.11 (1 H, d, H-8'), 4.00 (1 H, dd, $J_{4,5}$ 9.8 Hz, H-5), 3.88 (1 H, dd, $J_{7,7'}$ 11.5 Hz, H-7), 3.71 (1 H, dd, H-7'), 3.52 (1 H, d, H-4), 3.08 (1 H, d, $J_{1,1'}$ 14.1 Hz, H-1), 2.79 (1 H, dd, H-1'), 1.66, 1.53, and 1.38 (12 H, 3s, C*Me*$_2$); δ_C ($CDCl_3$): 137.58 (s, ArC), 130.31, 128.71 and 128.78 (3d, ArC), 112.06 (s, ring *C*Me$_2$), 108.94 (s, side chain *C*Me$_2$), 84.03, 81.10, 77.26, 74.80 and 69.31 (5d, C-2, 3, 4, 5 and 6), 60.02, 59.56 and 54.18 (3t, C-1, 7, and 8), 28.05, 26.36, 25.34, and 23.32 (4q, C*Me*$_2$); *m/z* (NH_3 c.i.) 364 (*M*H$^+$, 100%), 232 ($PhCH_2N^+CH_2CH(OCMe_2)CH(O)CH$, 89) and 91 ($C_7H_7^+$, 18).

1a, 2a, 6a, 7a, 7aβ-1,2:6,7-Di-O-*isopropylidene-1,2,6,7-tetrahydroxypyrrolizidine* (**15**). — Compound **21**, (91 mg, 0.25 mmol) was dissolved in dry CH_2Cl_2 (15 mL). Dry pyridine (0.04 mL, 2 equiv) was added and the solution stirred at 0° under nitrogen. Methanesulphonyl chloride (0.03 mL, 1.5 equiv) was added slowly, and after 4 h the mixture was allowed to warm up to room temperature. After 24 h, t.l.c. (3:1 hexane–EtOAc) indicated a product at the baseline but no starting material (R_F 0.25). Evaporation of the solvent and trituration with Et_2O (2 × 5 mL) gave a white solid residue which was dissolved in EtOH (5 mL) and added to a mixture of pre-reduced Pd black (10%) in degassed EtOH (10 mL). The resultant mixture was stirred vigorously for 24 h at room temperature under H_2 and then filtered through Celite. Evaporation of the solvent gave a white solid residue which was dissolved in EtOAc (20 mL), washed with saturated aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Flash chromatography (eluant EtOAc, increasing polarity to 9:1 EtOAc–MeOH) yielded compound **15** (20 mg, 31%) as a pale-yellow oil having spectroscopic data identical to those already given.

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