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ENANTIOSPECIFIC SYNTHESIS OF POLHYDROXYLATED INDOLIZIDINES RELATED TO CASTANOSPERMINE:[1] (6R,7S,8aR)-6,7-DIHYDROXYINDOLIZIDINE AND (6R,7R,8S,8aR)-6,7,8-TRIHYDROXYINDOLIZIDINE.

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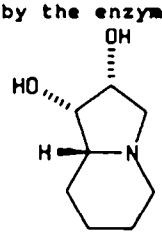
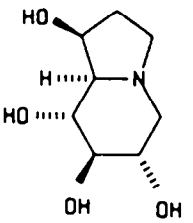
Enantiospecific syntheses of (6R,7S,8aR)-6,7-dihydroxyindolizidine (3) and (6R,7R,8S,8aR)-6,7,8-trihydroxyindolizidine (4) from methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (7) are reported. The two synthetic indolizidines (3) and (4) have been tested against a wide range of enzymes.

Introduction

Polyhydroxylated indolizidines are becoming increasingly more important as a result of their inhibitory action against various glycosidases, metastasis of some cancers, and replication of the human immunodeficiency virus (HIV).[1] A number of indolizidines have been synthesised in an attempt to establish possible structure-activity relationships.[2,3,4] For example, Colegate *et al.* have synthesised 8-deoxy-swainsonine (1) and found it to be a much weaker inhibitor of α-mannosidase than the parent alkaloid[5]; this has been attributed to the absence of the 8-hydroxyl group which is important for spatial recognition by the enzyme.



(1)

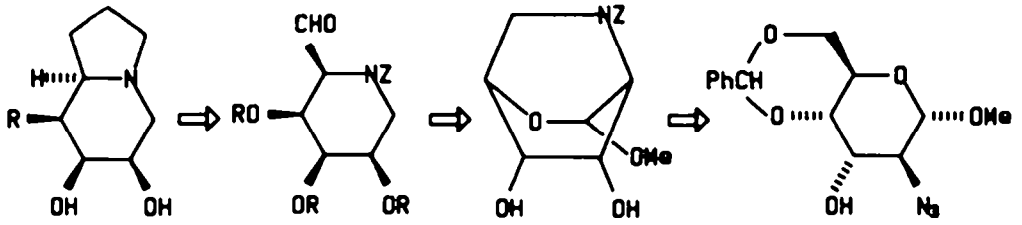


(2)

In the preceding paper[1] one approach to the synthesis of polyhydroxylated indolizidines related to castanospermine (2) from readily available carbohydrates was described. Herein we report another approach to the synthesis of these compounds in which the aldehyde (C-1) of the sugar corresponds to C-1 of the indolizidine. This work has been published in a preliminary communication.[4]

Results and Discussion

Retrosynthetic analysis of (4) required the construction of hydroxylated piperidine (5), which would be made from the key intermediate bicyclic methyl 2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (6) (Scheme 1). In order to form the bicycle (6) a leaving group at C-6 would be displaced by a 2-amino function so that methyl 2-azido-4,6-O-benzylidene-α-D-altropyranoside (7), available from methyl α-D-glucopyranoside in four steps[6], was the required starting compound.



(3) R=H (5) (6) (7)

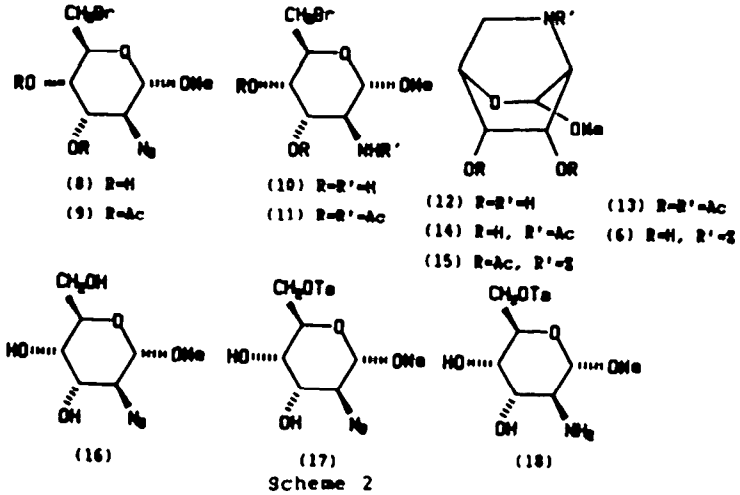
(4) R=OH

Scheme 1

The key intermediate (6) was made in two ways based on procedures by Hullar[7] and Meyer zu Reckendorf.[8] Thus reaction of the azide (7) with *N*-bromosuccinimide and barium carbonate in refluxing carbon tetrachloride, according to the Hanessian-Hullar procedure[9], afforded a mixture of two products as judged by t.l.c. (Scheme 2). These compounds proved to be a mixture of the 4-*O*- and 3-*O*-benzoyl bromides, resulting from participation of the 4-*O*-benzoyl group, since de-*O*-benzoylation with methanolic sodium methoxide yielded a single product, namely methyl 2-azido-6-bromo-2,6-dideoxy-α-D-altropyranoside (8) [54% yield from (7)]. Confirmation for the structure of (8) was provided by the mass spectrum of the derived di-*O*-acetyl compound (9), which displayed ions at 368, 366 (M + 1) and 336, 334 (M - OMe). Catalytic hydrogenation, carried out over a period of three hours to minimise hydrogenolysis of the 5-bromo group, gave rise to the amine (10) (88% yield) which was characterised as the crystalline amide (11). The IR spectrum of (11) displayed bands at 3300 cm^{-1} (N-H stretch), and 1650 and 1530 cm^{-1} characteristic of amide I and amide II bands respectively. Cyclisation of the free amine (10) was accomplished by boiling in ethanol containing sodium acetate to afford crude (12) which was converted into methyl 3,4-di-*O*-acetyl-2,6-acetylimino-2,6-dideoxy-α-D-altropyranoside (13) for the purposes of characterisation. Confirmation that cyclisation had occurred was provided by the IR spectrum of (13) in which the amide II band at 1530 cm^{-1} was absent. However, as is typical of compounds containing a cyclic amide linkage the ^1H NMR spectrum of (13) was ill-resolved due to a mixture of rotamers[10] and was not improved by running the spectrum at higher temperatures. The 2,6-imino-altroside (12) was further characterised as the *N*-acetyl derivative (14). For the purposes of the synthesis the free bicycle (12) was reacted with benzyl-

chloroformate and sodium hydrogen carbonate in aqueous ethanol to affored the carbamate (6) in 59% yield from azide (8). Subsequent acetylation furnished the crystalline diacetate (15).

In an alternative route to the bicycle (6) the acetal (7) was hydrolysed to the known triol[8] (16) by brief treatment with aqueous acetic acid (76% yield). Selective tosylation furnished the 6-tosylate (17) and this was followed by catalytic hydrogenation to give the tosyl-amine (18) (63% yield),



(8) R=H
(9) R=Ac
(10) R=R'=H
(11) R=R'=Ac
(12) R=R'=H
(13) R=R'=Ac
(14) R=H, R'=Ac
(6) R=H, R'=Z
(15) R=Ac, R'=Z
(16)
(17)
(18)

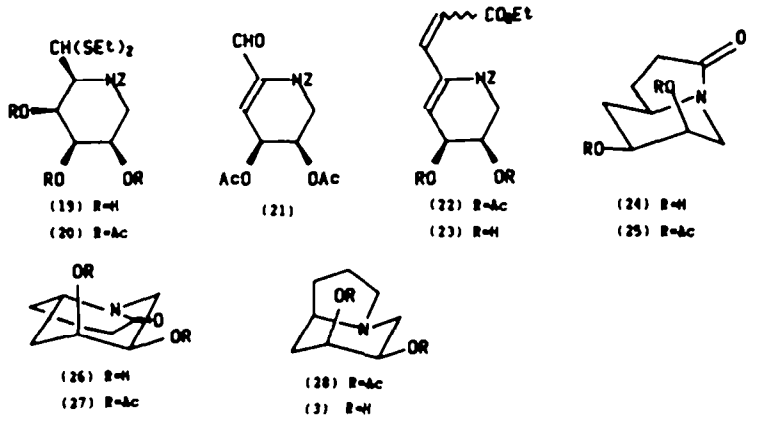
Scheme 2

which was used for the next step without further purification. Cyclisation of the amine (18), as described previously, and subsequent reaction with benzyl-chloroformate furnished methyl 2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (6) (64% yield from (17)), which presumably exists in a $^{2,5}B$ conformation.

As a means of accomplishing two carbon chain extension of the hydroxylated piperidine it was neccessary to hydrolyse the glycosidic linkage and trap the resulting hemiacetal as the aldehyde via a dithioacetal. Attempts to hydrolyse the glycoside (6) directly using aqueous acid or IR 120 (H^+) resin produced the desired hemiacetal, but this was converted into a number of components (t.l.c.) on work-up and the only isolable product was a pyridinium salt resulting from elimination of the elements of water from the hydroxylated piperidine. Comprehensive studies by Paulsen have shown that pyranose sugars in which the pyranose ring oxygen atom is replaced by nitrogen are very susceptible to acid catalysed elimination to give derivatives of 3-hydroxypyridine and/or Amadori rearrangement products.[11] To overcome this problem the glycoside (6) was treated with ethanethiol and concentrated hydrochloric acid in chloroform, which caused hydrolysis of the glycoside and formation of the diethyl dithioacetal (19) in a one-pot reaction (77% yield) (Scheme 3). Usually, the dithioacetal is rapidly formed under kinetic control and is slowly converted into the thioglycoside (thermodynamic product). In the case of (6) the resulting thioglycosides would not be as stable as the diethyl dithioacetal (19) which is the major product of the reaction. Acetylation of (19) yielded the tri-O-acetyl dithioacetal (20).

Subsequent dethioacetalation of (20) with mercuric chloride and cadmium carbonate in aqueous acetone[12] afforded a product (21), the ^1H NMR spectrum of which displayed only two acetyl resonances and an olefinic proton (δ 5.86, dd,

J 3.8, 0.8 Hz), suggesting that the 3-acetoxy group had eliminated under the reaction conditions to afford the α,β-unsaturated aldehyde (21). Although elimination had not been anticipated the synthesis was continued in order to



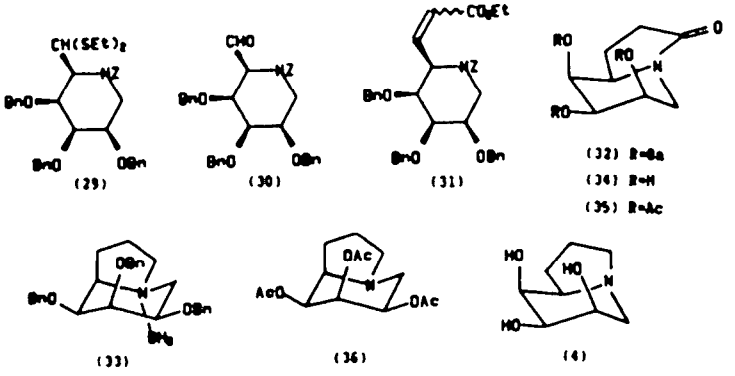
Scheme 3

produce a novel dideoxy-castanospermine analogue (3). Treatment of the α,β-unsaturated aldehyde (21) with carboethoxymethylene triphenylphosphorane furnished the Wittig adduct (22) (78% yield) as a mixture of *E*- and *Z*-isomers (*E*:*Z*, 3:2), as shown by the intensities of the two H-2 resonances. Catalytic hydrogenation of (22) caused removal of the benzyloxycarbonyl group and saturation of the double bond to give an intermediate amine which was not characterised. Attempts to cyclise the amine in the presence of sodium acetate afforded a poor yield of the desired lactam (25), possibly as a result of O to *N* acetyl migration. To improve the yield, the α,β-unsaturated ester (22) was de-O-acetylated with methanolic sodium methoxide to give the *E*-isomer (23) ($J_{2,3}$ 15.6 Hz). Catalytic hydrogenation and subsequent cyliisation produced a mixture of lactams (24, 26) in the ratio 15:1, that were epimeric at C-8a. The minor product (26) was obtained as a syrup after purification by flash chromatography and further fractionation afforded the major product (24) as a crystalline solid [71% yield from di-O-acetyl ester (22)]. The ^{1}H NMR spectrum of (24) demonstrated that it existed in the $^8C_5$ conformation, which is the only possible conformation due to mesomerism of the amide linkage. The H-5ax and H-5eq resonances appeared as a broad doublet and double doublet respectively ($J_{5ax,6}$ 0, $J_{5eq,6}$ 2.6, $J_{5ax,5eq}$ 13.8 Hz), indicating that H-6 was equatorial. The major product was identified as 2,3,4,5,8-pentadeoxy-4,8-imino-D-*arabino*-octono-1,4-lactam (24) since the H-8ax resonance appeared as a triplet (δ 2.11, $J_{8ax,8eq} = J_{8ax,8a} = J_{8ax,7} \approx$ 11 Hz), demonstrating that H-8a was axial and thus proving the configuration at C-8a to be *R*.[13] These assignments were corroborated by the 2D COSY spectrum of (24). Acetylation of the free lactam (24) afforded the di-O-acetyl-lactam (25) as a highly crystalline solid [60% from ester (22)]. Acetylation of the minor product (26) produced a syrupy diacetate (27), the ^{1}H NMR spectrum of which showed that the compound existed in the $^5C_8$ conformation. The H-6 proton, which is axial, resonated as a double double doublet ($J_{5ax,6}$ 11.3, $J_{5eq,6}$ 2.6, $J_{6,7}$ 2.8 Hz) and this information, together with H-5ax (δ 3.01, t, $J_{5ax,5eq}$ 12.5 Hz), demonstrated that the lactam was 6,7-di-O-acetyl-2,3,4,5,8-penta-deoxy-4,8-imino-D-*ribo*-octono-

1,4-lactam (27).[13]

Reduction of the lactam (25) by treatment with borane-dimethylsulphide gave rise initially to the borane-indolizidine complex[14] which decomposed on standing to the diacetoxy-indolizidine (28) in 77% yield. The ^{1}H NMR spectrum of (28) indicated that it existed in the $^5C_8$ conformation since H-5ax resonated as a double doublet ($J_{5ax,5eq}$ 13.1, $J_{5ax,6}$ 7.8 Hz). Conventional de-O-acetylation of (28) with methanolic sodium methoxide completed the synthesis of (6R,7S,8aR)-6,7-dihydroxy-indolizidine (3) (79% yield), the ^{1}H NMR spectrum of which was not very informative due to the presence of many methylene protons. However, it was possible to observe that (3) existed in the $^5C_8$ conformation with H-5ax (δ 3.46, dd, $J_{5ax,5eq}$ 12.6, $J_{5ax,6}$ 8 Hz) and H-5eq (δ 3.22, dd, $J_{5eq,6}$ 4 Hz).

In order to synthesise the desired trihydroxy-indolizidine (4) diethyl dithioacetal (19) was protected as the tri-O-benzyl derivative (29) (benzyl bromide and sodium hydride in *N,N*-dimethylformamide) in 79% yield (Scheme 4). Dethioacetalation afforded the tri-O-benzyl aldehyde (30) as a crystalline compound in almost quantitative yield, and subsequent reaction with the Wittig reagent carboethoxymethylene triphenylphosphorane yielded the syrupy α,β-unsaturated ester (31) (82% yield). Initially the ester (31) was subjected to catalytic hydrogenation, a process that effected hydrogenolysis of the benzyloxycarbonyl group and saturation of the double bond (but not



Scheme 4

hydrogenolysis of the benzyl groups), to give an amine which was cyclised in the usual way to the lactam (32) (63% yield). As was the case with the di-O-acetyl-lactam (25) the tri-O-benzyl-lactam (32) also adopted the $^8C_5$ conformation. Reduction of the tri-O-benzyl-lactam (32) with borane-dimethylsulphide[14] afforded the borane-indolizidine complex (33) as a stable compound (88% yield), the ^{1}H NMR spectrum of which showed that it existed in the $^5C_8$ conformation. However, hydrogenolysis of (33) in the presence of acetic acid led to a complex mixture of products.

Hydrogenolysis of tri-O-benzyl-lactam (32) in methanol containing acetic acid proceeded smoothly to afford the triol (34) as a crystalline compound (96% yield) and subsequent acetylation produced tri-O-acetyl-lactam (35) in 80% yield from (32). The ^{1}H NMR spectrum of triol (34) was completely amenable to a first order analysis and the 2D COSY emphasised spectrum showed a long-range W coupling between H-6 and H-8.[13] Reduction of the lactam (35) was carried out with borane-dimethylsulphide to give triacetoxy-indolizidine (36)

(78% yield), which existed in the $^{5}C_{8}$ conformation as shown by the ^{1}H NMR spectrum (H-5ax, t, $J_{5ax,eq}$ 12, $J_{5ax,6}$ 10 Hz). This is not surprising because once the rigidity imposed by the lactam carbonyl has been released the compound can adopt a conformation with two of the acetoxy groups taking up equatorial positions. The synthesis of (6R,7R,8S,8aR)-6,7,8-trihydroxy-indolizidine (4) was completed by de-*O*-acetylation of (36) to furnish the synthetic indolizidine as a syrup in 92% yield. The diagnostic H-5 resonances (H-5ax, dd, $J_{5ax,5eq}$ 11.7, $J_{5ax,6}$ 1.5 Hz; H-5eq, dd, $J_{5eq,6}$ 2.8 Hz) demonstrated that (4) adopted the $^{8}C_{5}$ conformation, possibly as a result of favourable hydrogen-bonding interactions. The assignments of the NMR spectrum were confirmed by a 2D COSY spectrum.[15]

Glycosidase Inhibition[16,17]

The dihydroxy- and trihydroxy-indolizidines (3, 4) were tested against a wide range of enzymes originating from aqueous extract of human liver. Using 4-methylumbelliferyl glycosides as substrates (3) actually *enhanced* the activity of the following enzymes: α-glucosidase (24%), α-fucosidase (27%), α-mannosidase (15%) and α-galactosidase (15%). Dihydroxy-indolizidine (3) proved to be a weak inhibitor of β-glucosidase (29%) and β-galactosidase (21%).

The trihydroxy-indolizidine (4) functioned as a weak inhibitor of β-galactosidase (26%), β-*N*-acetylhexosaminidases (23%) and α-fucosidase (21%). It is surprising that (3) actually enhances the activity of some enzymes, but not unexpected that it functions as a feeble glycosidase inhibitor because it appears that a decrease in the degree of deoxygenation of hydroxylated indolizidines results in a decrease in the potency of enzyme inhibition. Note the lack of glycosidase inhibition by 8-deoxy-swainsonine (1)[5]. Although trihydroxy-indolizidine (4) was shown to be a weak enzyme inhibitor, these results testify to the fact that it is not yet possible to design and synthesise hydroxylated indolizidines that will inhibit specific enzymes.

Experimental

Unless otherwise stated optical rotations were determined at room temperature (18-20°C) in 1 dm tubes on a Perkin Elmer 141 automatic polarimeter. ^{1}H NMR spectra were recorded either on a Bruker WH-400 (400 MHz), a Bruker WH-250 (250 MHz) or on a Nicolet NT-200 (200 MHz) spectrometer, and ^{13}C NMR spectra were recorded on a Bruker WP-60 (15.1 MHz) or WM-250 (61.3 MHz) spectrometer. All NMR spectra were run in deuteriochloroform unless stated otherwise. In all cases tetramethylsilane was used as internal standard. Mass spectra were determined on a Kratos MS-25 spectrometer by electron impact at 70 eV. Mass spectra of some of the more polar compounds were determined by the FAB technique. Melting points were measured on a Kofler hot-stage and are uncorrected. Microanalyses were obtained from either King's College, Kensington Campus or The London School of Pharmacy. Reactions were monitored by t.l.c. on silica gel ready-coated aluminium plates (Merck 5554). Spots were visualised by spraying with 5% concentrated sulphuric acid in ethanol, followed by heating. Flash chromatography was performed on Merck Kieselgel 60 (230-400 mesh) at a pressure of 5-20 p.s.i. Acetylations were carried out by dissolving the compound in pyridine (5-10 mL per mmol) and

adding excess acetic anhydride. The reaction was worked-up by pouring it into ice-water and extracting into chloroform. The organic layer was then washed with 10% hydrochloric acid, saturated sodium hydrogen carbonate solution and water, and finally dried over anhydrous magnesium sulphate. Diethyl ether was dried over sodium wire and tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Re-distilled light petroleum (b.p. 40-60°) was used throughout.

Methyl 2-azido-6-bromo-2,6-dideoxy-α-D-altropyranoside (8). To a solution of the azide (7) (3.2 g, 10.4 mmol) in carbon tetrachloride (120 mL) was added *N*-bromosuccinimide (2.4 g, 13.6 mmol), barium carbonate (2.26 g, 11.5 mmol) and a few crystals of benzoyl peroxide. The resulting mixture was heated under reflux for 2.5 h when t.l.c. (light petroleum-ethyl acetate, 1:1) showed the presence of a slightly faster-moving product. After filtering the suspension through Hyflo Supercell and evaporating to dryness, the residue was dissolved in ether (150 mL), washed with water (3 x 15 mL), dried ($MgSO_4$) and evaporated to a syrup. Flash chromatography of the crude reaction mixture (light petroleum-ethyl acetate, 1:1) produced two products corresponding to methyl 2-azido-3-*O*-benzoyl- and methyl 2-azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-altropyranoside (2.7 g, 67%). The above mixture was dissolved in dry methanol containing sufficient sodium methoxide to give a pH of 9 according to Universal indicator paper. The reaction mixture was left for 1 h at room temperature when t.l.c. (light petroleum-ethyl acetate, 2:1) showed the presence of a single slower-moving product. The reaction mixture was neutralised with Amberlite IR-120 (H^+) resin, filtered and evaporated to dryness. Flash chromatography with light petroleum-ethyl acetate (5:1) eluted methyl benzoate and subsequently light petroleum-ethyl acetate (1:1) gave the 6-bromo-altroside (8) (1.6 g, 81%) as a syrup, $[\alpha]_D$ +75.7° (c 1.1, chloroform). ν_{max} 2100 cm^{-1}. (Found: C, 29.81; H, 4.10; N, 14.66. $C_7H_{12}BrN_3O_4$ requires: C, 29.80; H, 4.29; N, 14.90%).

Methyl 3,4-di-O-acetyl-2-azido-6-bromo-2,6-dideoxy-α-D-altropyranoside (9). Acetylation of (8) with acetic anhydride and pyridine in the usual manner gave the diacetate (9) as a syrup, $[\alpha]_D$ +58.8° (c 1.1, chloroform). ν_{max} 2110 cm^{-1}. Mass spectrum: m/z 368, 366 (0.3, 0.4%), 336, 334 (13.0, 12.8), 308, 306 (2.8, 2.7) and 266, 264 (3.6, 3.8). (Found: C, 36.35; H, 4.42; N, 11.29. $C_{11}H_{16}BrN_3O_6$ requires: C, 36.08; H, 4.41; N, 11.48%).

Methyl 2-acetamido-3,4-di-O-acetyl-6-bromo-2,6-dideoxy-α-D-altropyranoside (11). The azide (8) (5 g) was dissolved in absolute ethanol and hydrogenated at 45 p.s.i. in the presence of 10% palladium on charcoal for 3 h. The catalyst was filtered off and the filtrate evaporated to yield the amine (10) as a foam (4 g, 88%). Acetylation of the free amine (10) in the usual way gave the bromo-amide (11) as a crystalline solid, m.p. 130-132° (from ethanol), $[\alpha]_D$ +68.4° (c 1.1, chloroform). ν_{max} 3300, 1735, 1650, 1530 cm^{-1}. ^1H NMR δ 6.19 (d, 1H, NH, $J_{2,NH}$ 8.9 Hz), 5.25 (t, 1H, H-3, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 3.6 Hz), 4.99 (dd, 1H, H-4, $J_{4,5}$ 9.5 Hz), 4.62 (s, 1H, H-1), 4.33 (dd, 1H, H-2, $J_{1,2}$ 0 Hz), 4.31 (ddd, 1H, H-5, $J_{5,6a}$ 2.7 Hz, $J_{5,6b}$ 6.6 Hz), 3.57 (dd, 1H, H-6a, $J_{6a,6b}$ 11.2 Hz), 3.45 (dd, 1H, H-6b), 3.45 (s, 3H, OMe), 2.12 (s, 3H, NAc) and 2.02 (s, 6H, OAc). Mass spectrum: m/z 384, 382 (5.6, 6.0%), 352, 350 (1.1,

1.3) and 264, 262 (1.4, 1.6). (Found: C, 40.90; H, 5.18; N, 3.37. $C_{13}H_{20}BrNO_7$ requires: C, 40.85; H, 5.24; N, 3.67%).

Methyl 3,4-di-O-acetyl-2,6-acetylimino-2,6-dideoxy-α-D-altropyranoside (13). To the syrupy free amine (10) (3.4 g), dissolved in absolute ethanol (150 mL), was added sodium acetate (1.7 g) and the mixture was heated under reflux overnight with stirring. The solvent was evaporated, the residue extracted thrice with boiling ethyl acetate, filtered and the filtrate concentrated to yield syrupy methyl 2,6-dideoxy-2,6-imino-α-D-altropyranoside (12).

The imino-sugar (12) was immediately acetylated in the usual way to give syrupy (13). Elution from a silica gel column with ethyl acetate-light petroleum (2:1) gave the analytical sample, $[\alpha]_D$ +7.8° (c 0.6, chloroform). ν_{max} 1740, 1655 cm^{-1}. Mass spectrum: m/z 302 (0.9%), 301, 270 (0.6) and 43 (100). (Found: C, 51.23; H, 6.28; N, 4.41. $C_{13}H_{19}NO_7$ requires: C, 51.82; H, 6.36; N, 4.65%).

Methyl 2,6-acetylimino-2,6-dideoxy-α-D-altropyranoside (14). Reaction of the 2,6-imino-altroside (12) with acetic anhydride in ethanol, followed by purification by flash chromatography (chloroform-methanol, 10:1) gave the *N*-acetyl derivative (14) as a crystalline solid, m.p. 146-148°, $[\alpha]_D$ -13.5° (c 0.8, chloroform). ν_{max} 3520, 3360, 1620 cm^{-1}. (Found: C, 49.93; H, 7.03; N, 6.26. $C_9H_{15}NO_5$ requires: C, 49.76; H, 6.96; N, 6.45%).

Methyl 2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (6). To a chilled solution of 2,6-imino-altroside (12) (1.2 g) in 50% aqueous ethanol (20 mL) containing sodium bicarbonate (0.9 g) was added benzyl chloroformate (0.7 mL). After stirring for 2 h t.l.c. (ethyl acetate) showed the presence of a major faster-moving product together with several minor faster-moving products. The reaction mixture was poured into water and extracted with ethyl acetate (4 x 15 mL), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate-acetone, 9:1) to give syrupy (6) [1.05 g, 67% overall from (10)], $[\alpha]_D$ -9.6° (c 1.2, chloroform). (Found: C, 58.10; H, 6.26; N, 4.11. $C_{15}H_{19}NO_6$ requires: C, 58.25; H, 6.19; N, 4.53%).

Methyl 2-azido-2-deoxy-α-D-altropyranoside (16). The azide (7) (20 g) was suspended in 20% aqueous acetic acid (250 mL) and heated at 80° for 1 h, when t.l.c. (chloroform-methanol, 5:1) indicated the presence of a single slower-moving product. Evaporation and finally co-evaporation with toluene gave the 2-azido-altroside (16) (10.8 g, 76%), which crystallised from ethyl acetate. Recrystallisation from the same solvent gave the pure azide, m.p. 137-138°, $[\alpha]_D$ +64.1° (c 1.0, methanol). Lit.[8] m.p. 137-138°, $[\alpha]_D$ +42.5° (DMSO). ν_{max} 2100 cm^{-1}.

Methyl 2-azido-2-deoxy-6-O-tosyl-α-D-altropyranoside (17). To a chilled solution of the 2-azido-altroside (16) (7.3 g, 33 mmol) in anhydrous pyridine (75 mL) was added dropwise a solution of toluene-*p*-sulphonyl chloride (7.9 g, 41 mmol) in pyridine, and the mixture was stirred overnight. T.l.c. (ethyl acetate) showed a major faster-moving product and some starting material. After pouring into ice-water the reaction mixture was extracted with chloroform (3 x 50 mL) and washed successively with 10% aqueous hydrochloric

acid, saturated sodium bicarbonate solution and finally water. The combined chloroform layers were dried ($MgSO_4$) and evaporated to a syrup. The crude syrup was chromatographed with ethyl acetate-light petroleum (3:2) as solvent to give the crystalline tosylate (17) (7.8 g, 63%), m.p. 90-91°, $[\alpha]_D$ +51.8° (c 1.0, chloroform). ν_{max} 3440, 2110, 1590, 1360, 1190. (Found: C, 44.94; H, 5.14; N, 11.30. $C_{14}H_{19}N_3O_7S$ requires: C, 45.04; H, 5.13; N, 11.25%).

Methyl 2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (6). The azide (17) (7.8 g) was dissolved in ethanol and hydrogenated at 45 p.s.i. in the presence of 10% palladium on charcoal overnight. After this time t.l.c. (ethyl acetate) showed a non-migrating component to be present. The catalyst was filtered off and the filtrate evaporated to afford the amine (18) as a foam (6.6 g, 91%). To a solution of the above amine (18) in ethanol was added sodium acetate (3.3 g) and the mixture was heated under reflux overnight. T.l.c. (butanol-pyridine-water, 10:3:3) showed a slower-moving product. The solvent was evaporated, the residue extracted thrice with boiling ethyl acetate, filtered and the filtrate evaporated to afford syrupy (12) (4.7 g). To a solution of (12) (4.7 g) in 50% aqueous ethanol (50 mL) containing sodium bicarbonate (3.3 g) was added benzyl chloroformate (2.7 mL). After stirring for 2 h t.l.c. (ethyl acetate) indicated the presence of a major faster-moving product together with several other minor faster-moving components. The solvent was evaporated, the residue extracted with ethanol, filtered and the filtrate evaporated to dryness. The residue was purified by elution from a column of silica gel with ethyl acetate-light petroleum (3:2) to give syrupy (6) [4.1 g, 70% overall yield from (18)], $[\alpha]_D$ -9.3° (c 1.0, chloroform). ν_{max} 1700 cm^{-1}. (Found: C, 58.10; H, 6.26; N, 4.11. $C_{15}H_{19}NO_6$ requires: C, 58.25; H, 6.19; N, 4.53%).

Methyl 3,4-di-O-acetyl-2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (15). Acetylation of (6) in the usual manner gave a syrup which was purified by flash chromatography (light petroleum-ethyl acetate, 1:1) to yield the di-O-acetyl derivative (15) as a crystalline solid, which had m.p. 70-72° (from ethanol), $[\alpha]_D$ -8.6° (c 0.6, chloroform). ν_{max} 1740, 1705 cm^{-1}. Mass spectrum: m/z 393 (0.1%), 362 (0.2), 334 (0.2), 273 (4.8), 91 (100) and 43 (27.9). (Found: C, 57.85; H, 5.91; N, 3.24. $C_{19}H_{23}NO_8$ requires: C, 58.01; H, 5.89; N, 3.56%).

2,6-Benzyloxycarbonylimino-2,6-dideoxy-D-altrose diethyl dithioacetal (19). To a chilled solution of the 2,6-imino-altroside (7) (1.0 g) in chloroform (5 mL) was added ethanethiol (1.0 mL) followed by concentrated hydrochloric acid (0.4 mL). The reaction mixture was stirred for 7-9 h when t.l.c. (ethyl acetate) showed a faster-moving product and the absence of starting material. The reaction mixture was neutralised by the addition of ice and saturated sodium bicarbonate solution, extracted with chloroform (3 x 15 mL) and finally dried ($MgSO_4$) to give the syrupy diethyl dithioacetal (19). Flash chromatography of the syrup (ether) gave the analytical sample (1.0 g, 77%), $[\alpha]_D$ +75.1° (c 1.1, chloroform). (Found: C, 53.68; H, 6.69; N, 3.29. $C_{18}H_{27}NO_5S_2$ requires: C, 53.84; H, 6.78; N, 3.49%).

Acetylation of the dietyl dithioacetal (19) according to the usual

procedure gave the syrupy tri-*O*-acetyl derivative (20), which was purified by flash chromatography (light petroleum-ether, 1:1), $[\alpha]_D$ +98.3° (c 1.0, chloroform). ν_{max} 1740, 1700 cm^{-1}. Mass spectrum: m/z 528, 467 (5.7%), 393 (7.3), 135 (28.8), 91 (100) and 43 (24.7). (Found: C, 54.50; H, 6.36; N, 2.52. $C_{24}H_{33}NO_8S_2$ requires: C, 54.63; H, 6.30; N, 2.66%).

4,5-Di-O-acetyl-2,6-benzyloxycarbonylimino-2,3,6-trideoxy-aldehydo-D-erythro-hex-2-enose (21). To a solution of the acetylated dithioacetal (20) (1.0 g, 1.90 mmol) in acetone (20 mL) and water (2 mL) was added mercuric chloride (1.25 g, 4.60 mmol) and cadmium carbonate (0.85 g, 4.93 mmol) and the mixture was heated under reflux (80°) for 30 min., when t.l.c. (ether-light petroleum, 3:1) showed the presence of a slower-moving component. After cooling, the reaction mixture was filtered through Hyflo Supercell to remove inorganic material and the filtrate evaporated. The residue was extracted with warm chloroform and filtered. The filtrate was washed with 10% aqueous potassium iodide solution (2 x 10 mL), water (10 mL), dried ($MgSO_4$) and concentrated to a syrup. T.l.c. showed that the syrup consisted of two components which were converted into a single compound on standing. Flash chromatography (ether-light petroleum, 2:1) gave the α,β-unsaturated aldehyde (21), $[\alpha]_D$ +92.5° (c 1.1, chloroform). ν_{max} 1745, 1705, 1640 cm^{-1}. ^1H NMR δ 9.48 (s, 1H, H-1), 5.86 (dd, 1H, H-3, $J_{3,3}$ 3.7 Hz, $J_{3,5}$ 0.8 Hz), 5.59 (t, 1H, H-4, $J_{4,5}$ 3.9 Hz), 5.25 (m, 1H, H-5, $J_{5,6a}$ 6.7 Hz, $J_{5,6b}$ 2.6 Hz), 5.24 (d, 1H, $PhCH_2$), 5.19 (d, 1H, $PhCH_2$), 4.00 (dd, 1H, H-6a, $J_{6a,6b}$ 13.6 Hz), 3.79 (dd, 1H, H-6b), 2.1 (s, 3H, OAc) and 2.0 (s, 3H, OAc). ^{13}C NMR δ 185.4 (C-1), 140.7 (C-3), 116.7 (C-2), 65.2 (C-4), 64.9 (C-5) and 45.3 (C-6). Mass spectrum: m/z 362, 301 (1.4%), 91 (100) and 43 (18.6). (Found: C, 59.74; H, 5.45; N, 3.70. $C_{18}H_{19}NO_7$ requires: C, 59.83; H, 5.30; N, 3.88%).

Condensaton of (21) with carboethoxymethylene triphenylphosphorane. To a solution of the crude aldehyde mixture (21) (1.78 g, 4.93 mmol) in acetonitrile (50 mL) was added carboethoxymethylene triphenylphosphorane (2.60 g, 7.26 mmol). The mixture was heated under reflux for 1 h when t.l.c. (ether-light petroleum, 3:1) showed a single faster-moving major product. After concentration, the reaction product was fractionated on a dry-packed column of silica gel. Elution with light petroleum-ether (3:2) gave the syrupy ester (22) (1.65 g, 78%), $[\alpha]_D$ +134° (c 1, chloroform). ν_{max} 1730, 1700 cm^{-1}. ^1H NMR δ 7.32 (d, 1H, H-3t, $J_{2,3}$ 15.6 Hz), 6.68 (bd, 1H, H-3c, $J_{2,3}$ 11.9 Hz), 6.03 (d, 1H, H-2t), 5.78 (d, 1H, H-2c), 5.55 (t, 1H, H-6t, $J_{5,6}$ 4.2 Hz, $J_{6,7}$ 4.4 Hz), 5.53 (t, 1H, H-6c) and 5.43 (d, 1H, H-5t). Mass spectrum: m/z 431 (0.4%), 371 (1.6), 91 (100) and 43 (53.2). (Found: C, 61.23; H, 6.04; N, 2.96. $C_{22}H_{25}NO_8$ requires: C, 61.25; H, 5.84; N, 3.25%).

De-*O*-acetylation of the ester (20) (1.6 g) in methanol (60mL) containing a catalytic amount of sodium methoxide for 2 h afforded two slower-moving products, as judged by t.l.c. (chloroform-methanol, 10:1). The solution was filtered through a pad of silica gel and evaporated to give the free ester (23) as a crystalline solid (1.0 g, 78%), m.p. 124-126° (ethanol), $[\alpha]_D$ +113 (c 0.5, chloroform). ν_{max}1725, 1690 cm^{-1}. ^1H NMR δ 7.27 (d, 1H, H-3, $J_{2,3}$ 15.6 Hz), 6.00 (d, 1H, H-2), 5.54 (d, 1H, H-5, $J_{5,6}$ 3.9 Hz), 5.16 (s, 2H, $PhCh_2$), 4.28 (t, 1H, H-6, $J_{6,7}$ 4.3 Hz, $J_{5,6}$ 3.9 Hz), 4.20 (q, 2H, CO_2Et), 3.92 (m, 1H, H-7, $J_{7,8a}$ 2.7 Hz, $J_{7,8b}$ 8.3 Hz), 3.84 (dd, 1H, H-8a, $J_{8a,8b}$ 12.9 Hz), 3.59

(dd, 1H, H-8b) and 1.25 (t, 3H, CO_2Et). (Found: C, 61.88; H, 6.01; N, 3.94. $C_{18}H_{21}NO_6$ requires: C, 62.24; H, 6.09; N, 4.03%).

2,3,4,5,8-Pentadeoxy-4,8-imino-D-arabino-octono-1,4-lactam (24). The ester (23) (1.0 g) was dissolved in ethanol and hydrogenated at 45 p.s.i. in the presence of 10% palladium on charcoal for 6 h. T.l.c. (butanol-pyridine-water, 10:3:3) showed the absence of starting material and the presence of two major and one minor products. After filtering off the catalyst, sodium acetate (0.4 g) was added and the resulting solution boiled overnight, after which time t.l.c. (chloroform-methanol, 2:1) revealed the presence of a faster-moving minor product and a slower-moving major product. Flash chromatography (chloroform-methanol, 5:1) gave a minor product (26), which was subsequently acetylated (see below). Further fractionation afforded the crystalline lactam (24) [510 mg, 71% from the acetylated Wittig adduct (22)] as the major product, m.p. 136-137°, $[\alpha]_D$ -2.4° (c 0.5, methanol). ^1H NMR (pyridine-d_5 + D_2O) δ 4.55 (dd, 1H, H-5eq, $J_{5ax,5eq}$ 13.8 Hz, $J_{5eq,6}$ 2.6 Hz), 4.30 (m, 1H, H-6, $J_{5ax,6}$ 0 Hz, $J_{6,7}$ 2.7 Hz), 4.05 (ddd, 1H, H-7, $J_{7,8ax}$ 11.3 Hz, $J_{7,8eq}$ 4.6 Hz), 3.46 (m, 1H, H-8a, $J_{8ax,8a}$ 11.6 Hz, $J_{8eq,8a}$ 7 Hz, $J_{1a,8a}$ 4 Hz, $J_{1b,8a}$ 7 Hz), 2.89 (bd, 1H, H-5ax), 2.34 (m, 2H, H-2a, H-2b), 2.11 (q, 1H, H-8ax, $J_{8ax,8eq}$ 11.6 Hz) and 1.40 (m, 1H, H-1b, $J_{1a,1b}$ 13 Hz). (Found: C, 55.77; H, 7.51; N, 7.99. $C_8H_{13}NO_3$ requires: C, 56.13; H, 7.65; N, 8.18%).

6,7-Di-O-acetyl-2,3,4,5,8-pentadeoxy-4,8-imino-D-arabino-octono-1,4-lactam (25). Acetylation of the lactam (24) in the conventional way gave the diacetate (25) as a solid. Purification by flash chromatography afforded the analytical sample [564 mg, 60% from the acetylated Wittig adduct (22)], m.p. 130-132°, (ether) $[\alpha]_D$ -22.1° (c 0.6, chloroform). ν_{max} 1730, 1685 cm^{-1}. ^1H NMR (*inter alia*) δ 5.27 (m, 1H, H-6, $J_{5ax,6}$ 1.0 Hz, $J_{5eq,6}$ 2.6 Hz, $J_{6,7}$ 2.8 Hz), 4.99 (ddd, 1H, H-7, $J_{7,8eq}$ 4.6 Hz, $J_{7,8ax}$ 12.1 Hz), 4.27 (dd, 1H, H-5eq, $J_{5ax,5eq}$ 14.7 Hz), 3.66 (m, 1H, H-8a, $J_{8ax,8a}$ 11.5 Hz, $J_{8eq,8a}$ 7.5 Hz, $J_{1a,8a}$ 6.5 Hz), 2.92 (dd, 1H, H-5ax), 2.44 (m ,2H, H-2a, H-2b), 2.28 (m, 1H, H-1a) and 1.78 (q, 1H, H-8ax, $J_{8ax,8eq}$ 12 Hz). ^{13}C NMR δ 174.4 (C-3), 69.9 (C-6), 66.2 (C-7), 55.0 (C-8a), 42.0 (C-5), 32.4 (C-8), 29.9 (C-2) and 24.2 (C-1). Mass spectrum: m/z 256 (7.1%), 195 (9.1), 154 (23.2), 135 (80.1) and 43 (100). (Found: C, 56.51; H, 6.68; N, 5.47. $C_{12}H_{17}NO_5$ requires: C, 56.46; H, 6.71; N, 5.49%).

6,7-Di-O-acetyl-2,3,4,5,8-pentadeoxy-4,8-imino-D-ribo-octono-1,4-lactam (27). Conventional acetylation of the lactam (26) yielded the syrupy di-O-acetyl lactam (27), $[\alpha]_D$ +28.0° (c 0.4, chloroform). ^1H NMR (*inter alia*) δ 4.78 (ddd, 1H, H-6, $J_{5ax,6}$ 11.3 Hz, $J_{5eq,6}$ 5.8 Hz, $J_{6,7}$ 2.7 Hz), 4.14 (dd, 1H, H-5eq, $J_{5eq,5ax}$ 12.5 Hz), 3.78 (m, 1H, H-8a, $J_{1a,8a}$ 3.5 Hz, $J_{1b,8a}$ 7 Hz, $J_{8ax,8a}$ 11 Hz, $J_{8eq,8a}$ 7 Hz), 3.01 (t, 1H, H-5ax), 2.44 (m, 2H, H-2a, H-2b), 2.24 (m, 1H, H-8ax) and 1.58 (m, 1H, H-1b). Mass spectrum: m/z 256 (22.7%), 195 (2.6), 154 (12.9), 135 (59.4) and 43 (100). (Found: C, 56.61; H, 6.88; N, 5.69. $C_{12}H_{17}NO_5$ requires: C, 56.46; H, 6.71; N, 5.49%).

(6R,7S,8aR)-6,7-Diacetoxy-indolizidine (28). To a solution of the acetylated lactam (25) (51 mg, 0.2 mmol) in dry THF (10 mL) was added borane-dimethyl-sulphide complex (0.1 mL, 1.0 mmol) and the reaction mixture was kept under an

atmosphere of nitrogen overnight. T.l.c. (light petroleum-ethyl acetate, 2:1) then revealed a single faster-moving product. Water was carefully added to decompose excess reducing agent, the aqueous phase extracted with chloroform, dried ($MgSO_4$) and concentrated to a syrup. This was co-evaporated several times with methanol and then purified by column chromatography (light petroleum-ethyl acetate, 2:1) to give the diacetoxy-indolizidine (28) as white crystals (37 mg, 77%), m.p. 81-83°, $[\alpha]_D$ +8.6° (c 0.6, chloroform). ^1H NMR (*inter alia*) (benzene-d_6) δ 5.61 (m, 1H, H-6, $J_{5ax,6}$ 7.8 Hz, $J_{5eq,6}$ 4.3 Hz, $J_{6,7}$ 3.8 Hz), 5.13 (m, 1H, H-7, $J_{7,8ax}$ 6.9 Hz, $J_{7,8eq}$ 3.6 Hz), 3.00 (ddd, 1H, H-3a, $J_{3a,3b}$ 12 Hz, $J_{2a,3a}$ 7 Hz, $J_{2b,3a}$ 9.5 Hz), 2.90 (m, 1H, H-3b), 2.85 (dd, 1H, H-5eq, $J_{5eq,5ax}$ 13.1 Hz) and 2.72 (dd, 1H, H-5ax). ^{13}C NMR (benzene-d_6) δ 67.0 (C-6), 66.7 (C-7), 64.3 (C-8a), 61.5 (C-5), 52.8 (C-3), 28.6 (C-8), 27.0 (C-2) and 19.7 (C-1). Mass spectrum: m/z 241 (1.0%), 182 (13.3), 181 (6.9), 140 (15.8), 122 (74.6) and 43 (100). (Found: C, 59.60; H, 7.82; N, 5.77. $C_{12}H_{19}NO_4$ requires: C, 59.73; H, 7.94; N, 5.80%).

(6R,7S,8aR)-6,7-Dihydroxy-indolizidine. (3). To a solution of the acetylated indolizidine (28) (37 mg, 0.15 mmol) in methanol was added a catalytic amount of sodium methoxide. After 1 h t.l.c. (chloroform-methanol, 15:1) indicated a single slower-moving product. The reaction mixture was passed through a pad of silica gel and concentrated to afford dihydroxy-indolizidine (3) as a syrup (19 mg, 79%), $[\alpha]_D$ +10.4° (c 0.3, methanol). ^1H NMR (*inter alia*) (pyridine-d_5 + D_2O) δ 4.64 (m, 1H, H-6, $J_{5ax,6}$ 8 Hz, $J_{5eq,6}$ 4.0 Hz, $J_{6,7}$ 3 Hz), 4.25 (m, 1H, H-7), 3.58 (dt, 1H, H-3a, $J_{2a,3a}$ 7 Hz, $J_{2b,3a}$ 7Hz, $J_{3a,3b}$ 12 Hz), 3.46 (dd, 1H, H-5ax, $J_{5ax,5eq}$ 12.6 Hz) and 3.22 (dd, 1H , H-5eq). Mass spectrum (FAB): m/z 158 (100%, M + H), found: 158.1180. $C_8H_{15}NO_2$ requires: 158.1181.

3,4,5-Tri-O-benzyl-2,6-benzyloxycarbonylimino-2,6-dideoxy-D-altrose diethyl dithioacetal (29). To an ice-cold solution of the dithioacetal (19) (1.9 g) in *N,N*-dimethylformamide (20 mL) was added portionwise sodium hydride (1.4 g of a 60% dispersion in oil) immediately followed by the dropwise addition of benzyl bromide (4.0 mL). The reaction mixture was stirred for 2 h when t.l.c. (light petroleum-ether, 3:1) showed a major faster-moving product. Ethanol was added to decompose excess sodium hydride and the reaction mixture was poured into ice-water. The product was extracted with ether (3 x 40 mL) and the combined ethereal extracts were washed with water, dried ($MgSO_4$) and concentrated. The resulting syrup was purified by passage through a column of silica gel. Excess benzyl bromide was eluted with light petroleum-ether (15:1); light petroleum-ether (11:2) eluted the tri-*O*-benzyl derivative (29) as a syrup (2.5 g, 79%), $[\alpha]_D$ +71.6° (c 1.0, chloroform). ν_{max} 1690 cm^{-1}. (Found: C, 69.92; H, 6.83; N, 1.78. $C_{39}H_{45}NO_5S_2$ requires: C, 69.72; H, 6.75; N, 2.09%).

3,4,5-Tri-O-benzyl-2,6-benzyloxycarbonylimino-2,6-dideoxy-aldehydo-D-altrose (30). To a solution of the dithioacetal (29) (0.6 g, 0.89 mmol) in acetone (12 mL) and water (1 mL) was added mercuric chloride (0.6 g, 2.21 mmol) and cadmium carbonate (0.4 g, 2.32 mmol). The mixture was heated under reflux for 1 h when t.l.c. (light petroleum-ether, 2:1) showed the presence of a single slower-moving product. After cooling, the reaction mixture was filtered through Hyflo Supercell and the filtrate co-evaporated with toluene. The residue was extracted with warm chloroform, filtered, washed successively with

10% aqueous potassium iodide solution, water and finally dried ($MgSO_4$). Concentration of the filtrate gave the aldehyde (30) as a solid (0.47 g, 93%), m.p. 103-105° (ethanol), $[\alpha]_D$ +59.6° (c 1.1, chloroform). ν_{max} 1715, 1690 cm^{-1}. (Found: C, 74.34; H, 6.17; N, 2.30. $C_{35}H_{35}NO_6$ requires: C, 74.32; H, 6.24; N, 2.48%).

Ethyl 5,6,7-tri-O-benzyl-4,8-benzyloxycarbonylimino-2,3,4,8-tetradeoxy-D-altro-oct-2-enoate (31). To a solution of the aldehyde (30) (1.2 g, 2.12 mmol) in acetonitrile (30 mL) was added carboethoxymethylene triphenylphosphorane (1.5 g, 4.31 mmol) and the reaction mixture was heated under reflux for 16 h. After this time t.l.c. (light petroleum-ethyl acetate, 5:1) showed a faster moving product together with triphenylphosphine oxide and excess Wittig reagent. Ether was added to precipitate triphenylphosphine oxide, which was filtered and the filtrate concentrated to dryness. Flash chromatography (light petroleum-ether, 3:2) gave the syrupy α,β-unsaturated ester (31) as the E,Z-mixture (1.1 g, 82%), $[\alpha]_D$ +38.2° (c 1.0, chloroform). ν_{max} 1700 cm^{-1}. Mass spectrum: m/z 635, 544 (1.3%) and 91 (100). (Found: C, 73.48; H, 6.54; N, 2.09. $C_{39}H_{41}NO_7$ requires: C, 73.68; H, 6.50; N, 2.20%).

5,6,7-Tri-O-benzyl-2,3,4,8-tetradeoxy-4,8-imino-D-altro-octono-1,4-lactam (32). The α,β-unsaturated ester (31) (2.0 g) was dissolved in ethanol and hydrogenated (45 p.s.i.) in the presence of 10% palladium on charcoal for 18 h, when t.l.c. (ethyl acetate-acetone, 3:1) showed two products to be present. After filtering off the catalyst sodium acetate (0.3 g) was added and the mixture boiled for 20 h. T.l.c. then revealed the presence of a single component. After removal of the solvent the residue was extracted with boiling ethyl acetate (3 x 25 mL), filtered and the combined filtrates concentrated. Flash chromatography (ethyl acetate-acetone, 3:1) gave the lactam (32) as a syrup which crystallised on standing (0.9 g, 63%), m.p. 60-62° (ether-light petroleum), $[\alpha]_D$ -26.1° (c 0.6, chloroform). ν_{max} 1675 cm^{-1}. ^1H NMR δ 4.54 (dd, 1H, H-5eq, $J_{5ax,5eq}$ 14 Hz, $J_{5eq,6}$ 2.0 Hz), 3.93 (m, 1H, H-6, $J_{5ax,6}$ 0 Hz, $J_{6,7}$ 2.7 Hz), 3.83 (m, 1H, H-8, $J_{7,8}$ 2.7 Hz, $J_{8,8a}$ 2 Hz), 3.58 (dt, 1H, H-8a, $J_{1b,8a}$ 9 Hz), 3.52 (t, 1H, H-7), 2.66 (bd, 1H, H-5ax), 2.54 (m 1H, H-2a, $J_{2a,2b}$ 17 Hz), 2.27 (m, 1H, H-2b, $J_{1b,2b}$ 1 Hz), 2.10 (m, 1H, H-1a, $J_{1a,8a}$ 3.4Hz) and 1.98 (m, 1H, H-1b). Mass spectrum: m/z 458, 366 (2.9%) and 91 (100). (Found: C, 75.82; H, 6.79; N, 3.06. $C_{29}H_{31}NO_4$ requires: C, 76.12; H, 6.83; N, 3.06%).

(6R,7R,8S,8aR)-6,7,8-Tribenzyloxy-indolizidine-borane complex (33). To a solution of the tri-O-benzyl-lactam (32) (0.4 g, 0.88 mmol) in dry THF was added borane-dimethylsulphide complex (4.4 mL, 8.8 mmol of a 2 M solution in THF) and the reaction mixture was stirred overnight under an atmosphere of nitrogen. T.l.c. (light petroleum-ether, 3:1) revealed the presence of a single faster-moving product. Water was carefully added to destroy excess reagent and the reaction mixture was concentrated to a syrup. This was co-evaporated several times with methanol. Purification by flash chromatography (light petroleum-ether, 3:1) gave the tribenzyloxy-indolizidine-borane as a syrup (0.35 g, 88%), which crystallised on trituration with ethanol. Recrystallisation from the same solvent afforded (33) as white crystals, m.p. 60-62°, $[\alpha]_D$ +13.8° (c 0.8, chloroform). ^1H NMR δ 4,21 (ddd, 1H, H-6, $J_{5ax,6}$

11 Hz, $J_{5eq,6}$ 4 Hz, $J_{6,7}$ 2.8 Hz), 4.17 (t, 1H, H-7, $J_{7,8}$ 2.8 Hz), 4.07 (dd, 1H, H-8, $J_{8,8a}$ 5.8 Hz), 3.46 (m, 1H, H-8a), 3.31 (dt, 1H, H-3a, $J_{2a,3a}$ 10 Hz, $J_{2b,3a}$ 10 Hz, $J_{3a,3b}$ 12 Hz), 3.17 (ddd, 1H, H-3b), 3.07 (t, 1H, H-5ax, $J_{5ax,5eq}$ 11 Hz) and 2.88 (dd, 1H, H-5eq). Mass spectrum: m/z 443 (5.0%), 352 (40.1) and 91 (100). (Found: C, 75.97; H, 7.90; N, 2.93. $C_{29}H_{36}BNO_3$ requires: C, 76.15; H, 7.93; N, 3.06%).

2,3,4,8-Tetradeoxy-4,8-imino-D-altro-octono-1,4-lactam (34). To a solution of tri-*O*-benzyl-lactam (32) (0.4 g) in ethanol was added glacial acetic acid (1.5 mL) and 10% palladium on charcoal and the mixture was hydrogenated at 60 p.s.i. for 36 h. After this period t.l.c. (chloroform-methanol, 2:1) showed a single slower-moving product. The catalyst was filtered off and washed well with aqueous methanol and the combined washings concentrated to syrupy (34), which crystallised from ethanol (157 mg, 96%), m.p. 165-170°, $[\alpha]_D$ +18.8° (c 0.6, methanol). ^{1}H NMR (pyridine-d_5 + D_2O) δ 4.63 (dd, 1H, H-5eq, $J_{5ax,5eq}$ 13.8 Hz, $J_{5eq,6}$ 2.3 Hz), 4.39 (m, 1H, H-6, $J_{5ax,6}$ 0 Hz, $J_{6,7}$ 2.8 Hz), 4.13 (m 1H, H-8, $J_{7,8}$ 2.8 Hz, $J_{8,8a}$ 1.5 Hz), 4.01 (t, 1H, H-7), 3.65 (ddd, 1H, H-8a, $J_{1a,8a}$ 4 Hz, $J_{1b,8a}$ 9 Hz), 3.01 (bd, 1H, H-5ax), 2.62 (m, 1H, H-2a, $J_{1a,2a}$ 3 Hz, $J_{1b,2a}$ 6 Hz, $J_{2a,2b}$ 17 Hz), 2.40 (m, 1H, H-2b, $J_{1a,2b}$ 6 Hz, $J_{1b,2b}$ 11 Hz), 2.20 (m, 1H, H-1a, $J_{1a,1b}$ 13 Hz) and 1.91 (m, 1H, H-1b). (Found: C, 50.94; H, 7.09; N, 7.27. $C_8H_{13}NO_4$ requires: C, 51.33; H, 7.00; N, 7.48%).

5,6,7-Tri-O-acetyl-2,3,4,8-tetradeoxy-4,8-imino-D-altro-1,4-lactam (35). Acetylation of the free lactam (34) with pyridine and acetic anhydride gave the tri-*O*-acetyl lactam as a syrup. Purification by flash chromatography (ethyl acetate-acetone, 4:1) gave (35) [80% from the tri-*O*-benzyl-lactam (32)], which had $[\alpha]_D$ +24.6° (c 0.9, chloroform). ν_{max} 1735, 1670 cm^{-1}. ^{1}H NMR (*inter alia*) (benzene-d_6) δ 5.14 (m, 1H, H-6, $J_{5ax,6}$ 0 Hz, $J_{5eq,6}$ 1.9 Hz, $J_{6,7}$ 3.2 Hz), 5.05 (m, 1H, H-8, $J_{7,8}$ 3.2 Hz, $J_{8,8a}$ 2.7 Hz), 4.78 (t, 1H, H-7), 4.37 (dd, 1H, H-5eq, $J_{5eq,5ax}$ 14.7 Hz), 2.82 (dt, 1H, H-8a, $J_{1a,8a}$ 8.6 Hz, $J_{1b,8a}$ 2.7 Hz), 2.29 (bd, 1H, H-5ax), 2.14 (m, 1H, H-2a, $J_{2a,2b}$ 17 Hz) and 1.94 (m, 1H, H-2b). ^{13}C NMR (benzene-d_6) δ 173.6 (C-3), 69.6 (C-7), 69.4 (C-8), 66.8 (C-6), 56.9 (C-8a), 41.7 (C-5), 29.7 (C-2) and 19.1 (C-1). Mass spectrum: m/z 314 (3.5%, 253 (0.2), 212 (2.0), 194 (6.5), 193 (19.6) and 43 (100). (Found: C, 53.55; H, 6.21; N, 4.26. $C_{14}H_{19}NO_7$ requires: C, 53.67; H, 6.11; N, 4.47%).

(6R,7R,8S,8aR)-6,7,8-Triacetoxy-indolizidine (36). To a solution of tri-*O*-acetyl-lactam (35) (94 mg, 0.3 mmol) in dry THF was added borane-dimethyl-sulphide complex (0.2 mL, 2.0 mmol) and the reaction mixture was stirred overnight under an atmosphere of nitrogen. T.l.c. (light petroleum-ethyl acetate, 1:1) showed a faster-moving major product together with traces of deacetylated products. Water was added carefully and the solution was extracted with chloroform, dried ($MgSO_4$) and concentrated to a syrup. This was co-evaporated several times with methanol and then purified by flash chromatography (light petroleum-ethyl acetate, 1:1) to give (36) as a crystalline solid (70 mg, 78%). M.p. 138-140°, $[\alpha]_D$ +7.8° (c 0.5, chloroform). ^{1}H NMR (benzene-d_6) δ 5.79 (ddd, 1H, H-6, $J_{5ax,6}$ 10.4 Hz, $J_{5eq,6}$ 4.6 Hz, $J_{6,7}$ 3.3 Hz), 5.63 (t, 1H, H-8, $J_{7,8}$ 4 Hz, $J_{8,8a}$ 5 Hz), 5.61 (m, 1H, H-7), 3.32 (m, 1H, H-8a, $J_{1a,8a}$ 9 Hz, $J_{1b,8a}$ 9 Hz), 3.05 (dt, 1H, H-3a, $J_{2a,3a}$ 9.3 Hz, $J_{2b,3a}$ 9.3 Hz, $J_{3a,3b}$ 12.3 Hz), 2.80 (dd, 1H, H-5eq, $J_{5ax,5eq}$ 12 Hz), 2.74

(m, 1H, H-3b) and 2.56 (t, 1H, H-5ax). ^{13}C NMR (benzene-d_6) δ 67.8 (C-7), 66.5 (C-8), 65.6 (C-6), 65.4 (C-8a), 64.6 (C-5), 50.8 (C-3), 24.8 (C-2) and 19.5 (C-1). Mass spectrum: m/z 300 (14.2%), 299 (0.4), 240 (41.5), 239 (11.5) and 180 (31.5). (Found: C, 55.89; H, 7.23; N, 4.63. $C_{14}H_{21}NO_6$ requires: C, 56.18; H, 7.07; N, 4.68%).

(6R,7R,8S,8aR)-6,7,8-Trihydroxyindolizidine (4). To a solution of the triacetoxy-indolizidine (36) (90 mg) in methanol was added a catalytic amount of sodium methoxide. After 1 h t.l.c. (chloroform-methanol, 5:1) revealed only a single slower-moving component. The solution was passed through a pad of silica gel and the filtrate concentrated. Flash chromatography (chloroform-methanol, 5:1) gave the trihydroxy-indolizidine (4) as a syrup (48 mg, 92 %), $[\alpha]_D$ +10.1° (c 0.9, methanol). ^{1}H NMR (*inter alia*) (pyridine-d_5) δ 4.26 (m, 1H, H-6, $J_{5ax,6}$ 1.5 Hz, $J_{5eq,6}$ 2.8 Hz, $J_{6,7}$ 3.2 Hz), 4.15 (m, 1H, H-8, $J_{7,8}$ 3.2 Hz, $J_{8,8a}$ 0 Hz), 3.74 (t, 1H, H-7), 2.39 (dd, 1H, H-5eq, $J_{5eq,5ax}$ 11.7 Hz), 3.04 (t, 1H, H-3a, $J_{1a,8a}$ 8.4 Hz, $J_{1b,8a}$ 8.4 Hz), 2.21 (dd, 1H, H-5ax) and 1.82 (m, 1H, H-1b). Mass spectrum (FAB): m/z 174 (100%, M + H) found: 174.1132. $C_8H_{15}NO_3$ requires: 174.1130.

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