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ENANTIOSPECIFIC SYNTHESIS OF (6R,7S,8aR)-DIHYDROXYINDOLIZIDINE AND (6R,7R,8S,8aR)-TRIHYDROXYINDOLIZIDINE FROM D-GLUCOSE.

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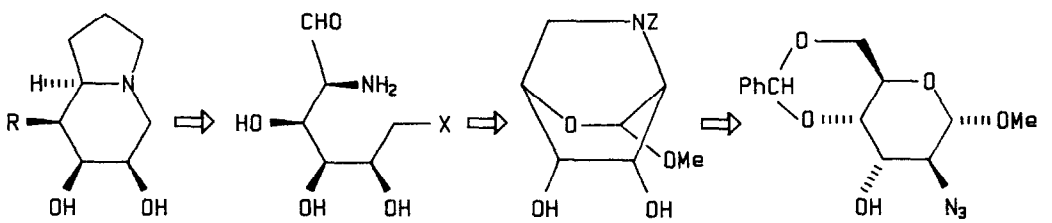
Summary: Enantiospecific syntheses of (6R,7S,8aR)-dihydroxyindolizidine (1) and (6R,7R,8S,8aR)-trihydroxyindolizidine (2) from readily available methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (5) are described.

The preceding paper[1] describes one approach to the enantiospecific synthesis of 1-deoxy-castanospermine from D-glucose. As a continuation of our interest in the synthesis of hydroxylated indolizidines related to castanospermine as potential glycosidase inhibitors, we now wish to report another approach to the synthesis of these compounds from carbohydrate precursors. Our intention was to utilise a carbohydrate in such a way that the aldehyde would correspond to C-1 of the indolizidine. A possible starting compound was chosen as methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (5), a compound that can be synthesised in large quantities.[2] The key step in the synthesis involved displacement of a C-6 leaving group by a 2-amino function (3) to form the key intermediate methyl 2,6-dideoxy-2,6-imino-α-D-altropyranoside (4) and this would be followed by a two carbon chain extension (Scheme 1).



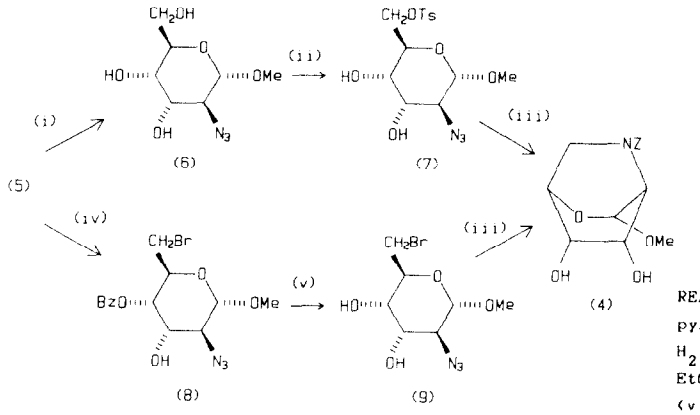
(1) R=H (2) R=OH (3) X=OTs or Br (4) (Z=$CO_2CH_2C_6H_5$) (5)

SCHEME 1

Methyl 2,6-benzyloxycarbonylimino-2,6-dideoxy-α-D-altropyranoside (4) was synthesised by two routes based on procedures by Meyer zu Reckendorf[3] and Hullar.[4] Hydrolysis of the benzylidene acetal (5) using aqueous acetic acid (Scheme 2) afforded the known triol (6) (76% yield), which underwent selective

tosylation to yield methyl 2-azido-2-deoxy-6-*O*-tosyl-α-D-altropyranoside (7) (63% yield). Catalytic hydrogenation and subsequent cyclisation in the presence of sodium acetate gave the 2,6-imino-altroside, which was isolated as the benzyloxycarbonyl derivative (4)[5] [64% yield from (7)].

Alternatively, treatment of the 2-azido-altroside (5) with *N*-bromosuccinimide (NBS), according to the Hanessian-Hullar procedure,[6] led to

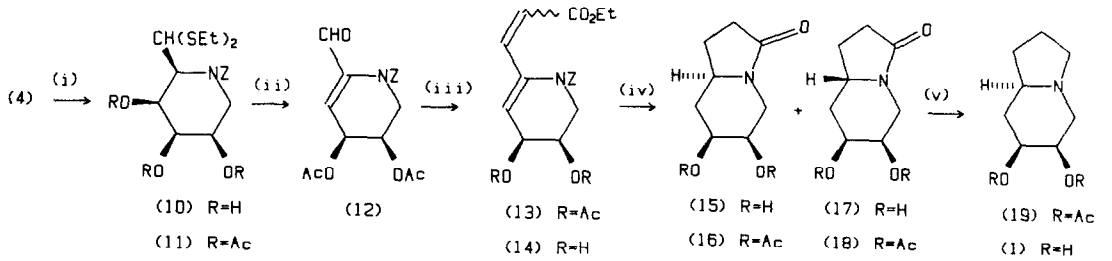


REAGENTS: (i) AcOH (20%)-H_2O (ii) TsCl, pyridine (iii) 10% Pd on charcoal, EtOH H_2; NaOAc, EtOH reflux; CbzCl, $NaHCO_3$, EtOH (50%)-H_2O (iv) NBS, $BaCO_3$, CCl_4 (v) NaOMe, MeOH

SCHEME 2

formation of methyl 2-azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-altropyranoside (8) and subsequent Zemplen de-*O*-benzoylation gave the diol (9) [54% from (5)]. Careful catalytic hydrogenation of azide (9) yielded methyl 2-amino-6-bromo-2,6-dideoxy-α-D-altropyranoside, which was used for the next step without purification; prolonged hydrogenation gave rise to the 6-deoxy-altroside as a result of hydrogenolysis of the primary bromide group. As before, cyclisation of the free amine in the presence of sodium acetate followed by nitrogen protection afforded (4) [59% from (9)].

When the 2,6-imino-altroside (4) was treated with ethanethiol and concentrated hydrochloric acid over a period of 7-9 h, hydrolysis of the glycoside occurred together with formation of the required diethyl dithioacetal (10) in 77% yield (Scheme 3). Attempts to hydrolyse the glycoside (4) directly with aqueous acid led to formation of a pyridinium salt resulting from elimination of water from the hydroxylated piperidine; these findings are consistent with the work of Paulsen.[7] The diethyl dithioacetal (10) was converted into 3,4,5-tri-*O*-acetyl-2,6-benzyloxycarbonylimino-2,6-dideoxy-D-altrose diethyl dithioacetal (11) followed by dethioacetalation using mercuric chloride and cadmium carbonate in aqueous acetone[8] to give a compound (12), the ^{1}H NMR spectrum of which showed the presence of only two acetyl resonances and an olefinic proton. These findings suggested that the 3-acetoxy group had eliminated under the reaction conditions to afford the α,β-



(10) R=H
(11) R=Ac
(12)
(13) R=Ac
(14) R=H
(15) R=H
(16) R=Ac
(17) R=H
(18) R=Ac
(19) R=Ac
(1) R=H

(Z=$CO_2CH_2C_6H_5$)

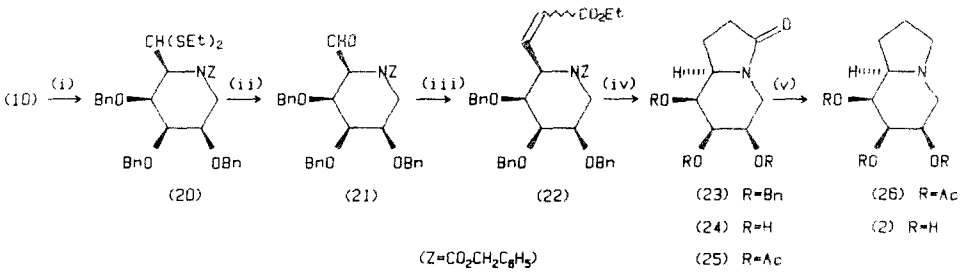
REAGENTS: (i) EtSH, HCl, $CHCl_3$; Ac_2O, pyridine (ii) $HgCl_2$, $CdCO_3$, Me_2CO (10%)-H_2O (iii) $Ph_3P{=}CHCO_2Et$, CH_3CN; NaOMe, MeOH (iv) 10% Pd on charcoal, H_2, EtOH; NaOAc, EtOH, reflux; Ac_2O, pyridine (v) BH_3SMe_2, THF; NaOMe, MeOH

SCHEME 3

unsaturated aldehyde (12). Although the elimination step was not anticipated it was decided to convert the aldehyde into the novel dihydroxyindolizidine (1).

Reaction of the α,β-unsaturated aldehyde (12) with carboethoxymethylene triphenylphosphorane yielded the ester (13) (78% yield) and subsequent de-*O*-acetylation led to the diol (14),[9] (78% yield). The next sequence involved catalytic hydrogenation, followed by cyclisation (sodium acetate) to afford a mixture of two compounds in the ratio 15:1 corresponding to the lactams epimeric at C-8a. As expected, 2,3,4,5,8-pentadeoxy-4,8-imino-D-*arabino*-octono-1,4-lactam (15) [71% from (13)] was identified as the major isomer, which resulted from delivery of hydrogen from the least hindered face. Acetylation of (15) afforded the di-*O*-acetyl derivative (16) [60% from (13)]. Acetylation of the minor product (17) afforded 6,7-di-*O*-acetyl-2,3,4,5,8-pentadeoxy-4,8-imino-D-*ribo*-octono-1,4,-lactam (18), the structure of which was readily deduced from the 250 MHz ^1H NMR spectrum. Treatment of di-*O*-acetyl lactam (16) with borane-dimethyl sulphide in THF resulted in reduction of the lactam carbonyl group to give (6R,7S,8aR)-diacetoxyindolizidine (19),[10] (77% yield). Finally, Zemplen de-*O*-acetylation afforded syrupy (6R,7S,8aR)-dihydroxyindolizidine (1).

In order to synthesise the desired trihydroxyindolizidine (2), the diethyl dithioacetal (10) was converted into syrupy 3,4,5-tri-*O*-benzyl-2,6-benzyloxycarbonylimino-2,6-dideoxy-D-altrose diethyl dithioacetal (20) (79% yield) (Scheme 4). Dethioacetalisation under identical conditions as before gave aldehyde (21) in near quantitative yield. Chain extension was accomplished by reaction of the aldehyde (21) with carboethoxymethylene triphenylphosphorane, which yielded the syrupy α,β-unsaturated ester (22) (82% yield). When the ester was subjected to catalytic hydrogenation followed by treatment with sodium acetate in refluxing ethanol, 5,6,7-tri-*O*-benzyl-2,3,4,8-tetradeoxy-4,8-imino-D-*altro*-octono-1,4-lactam (23) was obtained in 63% yield. Reaction



REAGENTS: (i) BnBr, NaH, DMF (ii) $HgCl_2$, $CdCO_3$, Me_2CO (10%)-H_2O (iii) $Ph_3P{=}CHCO_2Et$, CH_3CN; (iv) 10% Pd on charcoal, H_2, EtOH; NaOAc, EtOH, reflux, 10% Pd on charcoal, H_2, AcOH, 48h; Ac_2O, pyridine (v) BH_3SMe_2, THF; NaOMe, MeOH

SCHEME 4

of the tri-*O*-benzyl lactam (23) with hydrogen and palladium as catalyst in acetic acid gave the free lactam (24) in 96% yield, and this was followed by acetylation with acetic anhydride and pyridine to afford tri-*O*-acetyl-lactam (25), [80% from (23)]. Reduction of tri-*O*-acetyl-lactam (25) with borane-dimethylsulphide gave (6R,7R,8S,8aR)-triacetoxyindolizidine (26)[10] in 78% yield. The synthesis of the indolizidine was completed by de-esterification of (26) to afford syrupy (6R,7R,8S,8aR)-trihydroxyindolizidine (2).

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5. All new compounds reported herein were fully characterised by microanalysis, IR, ^1H and ^{13}C NMR, and mass spectrometry. Specific rotations were measured in $CHCl_3$ except where indicated otherwise. Physical data: (6), m.p. 137-138°, $[\alpha]_D$ +64.1° (MeOH); (7), m.p. 90-91°, $[\alpha]_D$ +51.8°; (9), $[\alpha]_D$ +75.5°; (4), $[\alpha]_D$ -9.6°; (10), $[\alpha]_D$ +75.1°; (14), m.p. 124-126°, $[\alpha]_D$ +113°; (15), m.p. 136-137°, $[\alpha]_D$ -2.4° (MeOH); (16), m.p. 130-132°, $[\alpha]_D$ -22.1°; (18), $[\alpha]_D$ +28.0°; (19), m.p. 81-83°, $[\alpha]_D$ +8.6°; (1), $[\alpha]_D$ +10.4° (MeOH); (21), m.p. 103-105°, $[\alpha]_D$ +71.6°; (23), m.p. 60-62°, $[\alpha]_D$ -26.1°; (24), m.p. 165-170°, $[\alpha]_D$ +18.8° (MeOH); (25), $[\alpha]_D$ +24.6°; (26), m.p. 138-140°, $[\alpha]_D$ +7.8°; (2), $[\alpha]_D$ +10.1° (MeOH).
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9. ^1H NMR indicated that the product was the *E*-isomer ($J_{2,3}$=15.6 Hz).
10. Treatment of tri-*O*-benzyl-lactam (23) with borane-dimethylsulphide afforded the tribenzyloxyindolizidine-borane complex as a stable compound, m.p. 60-62°, $[\alpha]_D$ +13.8°. However, no attempt was made to destroy the initially formed indolizidine-borane complexes resulting from reduction of lactams (16) and (25); these compounds gave satisfactory microanalyses, ^1H and ^{13}C NMR spectra indicating that the borane complex decomposed on standing.

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