# A Chiral Synthesis of Swainsonine from D-Glucose

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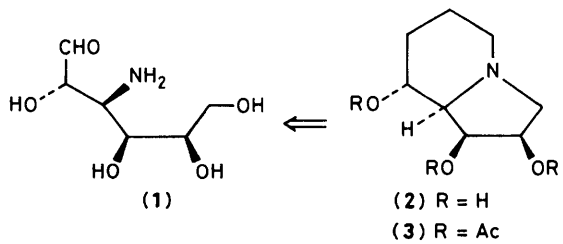
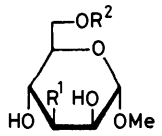
The synthesis of the alkaloid swainsonine is described starting from methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (readily available from D-glucose) in which all the chiral centres of the aminohexose are incorporated intact into the alkaloid.

Several hydroxylated indolizidine alkaloids have been isolated recently from plants and some micro-organisms.[1—5] One such compound, which is of considerable interest, is swainsonine (**2**) which was originally isolated from the legume *Swainsona canescens*[1] but has also been shown to be present in locoweed (*Autralgalus lentiginosus*)[2] and in the fungus *Rhizoctonia leguminicola*.[3] The compound is a potent inhibitor of mannosidase and disrupts the processing of glycoproteins. The alkaloid induces a condition similar to mannosidosis in cattle which graze on pastures containing these weeds.[6]

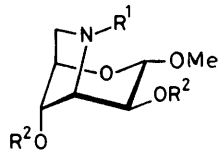



(**1**) (**2**) R = H (**3**) R = Ac

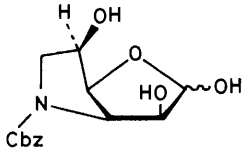
Retrosynthetic reasoning suggested that 3-amino-3-deoxy-D-mannose (**1**) would be a suitable chiral precursor of (**2**), since the formation of a 3,6-imino linkage and the addition of a simple '$-CH_2CH_2-$' unit between C-1 and N-3 would provide the required skeletal arrangement with the correct stereochemistry.



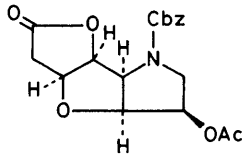
(4) $R^1 = NH_3Cl$, $R^2 = H$
(5) $R^1 = NHCbz$, $R^2 = p\text{-}MeC_6H_4SO_2$



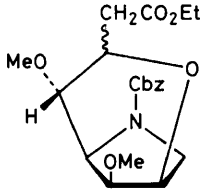
(6) $R^1 = R^2 = H$
(7) $R^1 = Cbz$, $R^2 = H$
(8) $R^1 = Cbz$, $R^2 = Me$



(9)



(10)



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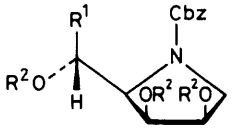
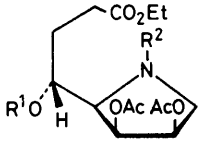
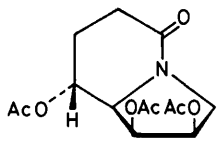


(12) $R^1 = CH(SEt)_2$, $R^2 = H$
(13) $R^1 = CH(SEt)_2$, $R^2 = Ac$
(14) $R^1 = CHO$, $R^2 = Ac$
(15) $R^1 = CH{=}CHCO_2Et$, $R^2 = Ac$



(16) $R^1 = Ac$, $R^2 = H$
(17) $R^1 = H$, $R^2 = Ac$



(18)

Cbz = $PhCH_2OCO$–

Methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (**4**) is readily available from methyl α-D-glucopyranoside in 20—25% yield[7] by the nitromethane dialdehyde cyclisation procedure, and was therefore the starting material of choice. Sequential *N*-benzyloxycarbonylation and selective tosylation of (**4**) gave the crystalline 6-*O*-toluene-*p*-sulphonate (**5**) in 82% overall yield. Attempts to form the 3,6-imine (**6**) directly from the latter by treatment with alkali failed to effect the required cyclisation, but when the *N*-benzyloxycarbonyl group was first removed by hydrogenolysis and the product boiled in ethanol containing sodium acetate a smooth cyclisation occurred and the 3,6-epimine (**6**) was formed which was isolated as its *N*-benzyloxycarbonyl derivative (**7**) in 52% overall yield from (**4**). Acid hydrolysis of (**7**) afforded the free crystalline 3,6-dideoxy-3,6-iminohexofuranose (**9**) {m.p. 138—139 °C, $[\alpha]_D$ −11° (methanol)} in 52% yield.

The addition of the $C_2$ unit was then attempted directly on the free hexose by condensation of (**9**) with ethoxycarbonylmethylenetriphenylphosphorane. The condensation proceeded with great ease, but subsequent Michael addition of the 4-OH to the double bond followed by lactonisation afforded a tricyclic lactone which was characterised as its highly crystalline *O*-acetyl derivative (**10**) {m.p. 165—167 °C, $[\alpha]_D$ −115° (chloroform)} which was of no further interest in the synthesis at hand but indicated the desirability of protecting the 2- and 4-hydroxy groups before attempting the Wittig reaction. However when the same sequence of reactions was repeated starting from the 2,4-di-*O*-methyl ether (**8**), the 5-hydroxy group then took part in Michael addition to give the syrupy bicyclic derivative (**11**) in good yield, showing that the Wittig reaction would only be successful if all three of the hydroxy groups at C-2, C-4, and C-5 were protected.

The 3,6-iminohexose (**9**) was condensed with ethanethiol in the presence of hydrochloric acid to give the diethyl dithioacetal (**12**) in 74% yield as a crystalline compound {m.p. 98—100°C, $[\alpha]_D$ −61° (chloroform)}, which was then converted into its syrupy tri-*O*-acetate (**13**). Subsequent dethioacetalation of (**13**) with mercury(II) chloride–cadmium carbonate proceeded smoothly to give the desired fully protected syrupy *aldehydo*-hexose (**14**) which then reacted with the phosphorane to give an apparently chromatographically homogeneous product. However, as in all these compounds, homogeneity was difficult to establish by n.m.r. spectroscopy because restriction of rotation about the amide bond gave complex spectra in most cases. However it was unimportant whether or not (**15**) was the *cis* or *trans* isomer since the next stage involved the saturation of the double bond. This was carried out over palladium-on-charcoal which also simultaneously removed the *N*-benzyloxycarbonyl group, to give, initially, the free amine (**16**) which then reacted further to give a 1:1 mixture of two products resulting from the nucleophilic attack of the amino group on two of the ester functions. One product was the desired cyclic lactam (**18**) {m.p. 143—145 °C, $[\alpha]_D$ −12° (chloroform)} and the other was the product of *O*→*N* acetyl migration (**17**).

Reduction of the cyclic lactam (**18**) with the borane·dimethylsulphide complex afforded a mixture of two products which were separated by chromatography. The slower-moving major component was isolated pure and shown to be tri-*O*-acetylswainsonine (**3**), by comparison of its $^1H$ n.m.r. spectrum with that reported in the literature.[3] The faster-moving product awaits identification.

Conventional *O*-deacetylation of the triacetate (**3**) with sodium methoxide afforded a quantitative yield of the highly crystalline swainsonine (**2**) {m.p. 146 °C, $[\alpha]_D$ −84° (methanol); lit.[3] m.p. 144—145 °C, $[\alpha]_D$ −87.2°} which was identical (mixed m.p., i.r., and t.l.c.) to an authentic specimen of (**2**) kindly provided by Dr. B. G. Winchester and confirms the absolute configuration. This represents the first total synthesis of swainsonine, which was achieved in an overall yield of 2.7% from (**4**).

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## References


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