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TOTAL SYNTHESIS OF (-)-SWAINSONINE, AN α-MANNOSIDASE INHIBITOR ISOLATED FROM *SWAINSONA CANESCENS*

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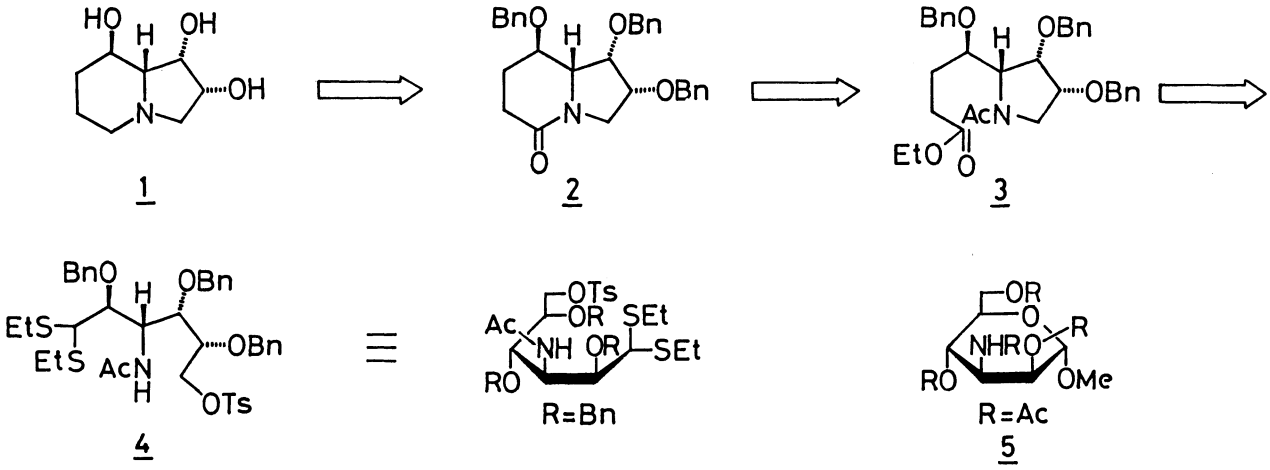
The alkaloidal toxin, (-)-swainsonine: (1S,2R,8R,8aR)-1,2,8-trihydroxyoctahydroindolizine has been synthesized stereoselectively starting from methyl 3-acetamido-2,4,6-tri-O-acetyl-3-deoxy-α-D-mannopyranoside in a 15 steps reaction.

(-)-Swainsonine (1) is an indolizidine alkaloid toxin newly isolated from *Swainsona canescens*,[1] *Astragalus lentiginosus*,[2] and *Rhizoctonia leguminicola*,[3] which exhibits remarkable physiological effects such as depression of nervous and muscular in coordination in animals, when they are feeded with toxin-infected feeds. Also the toxin shows an inhibitory activity against α-mannosidase enzymes. Owing to the interesting biological activities, the toxin has attracted attentions of several research groups from a view of structural determination[1,3] and biosynth-

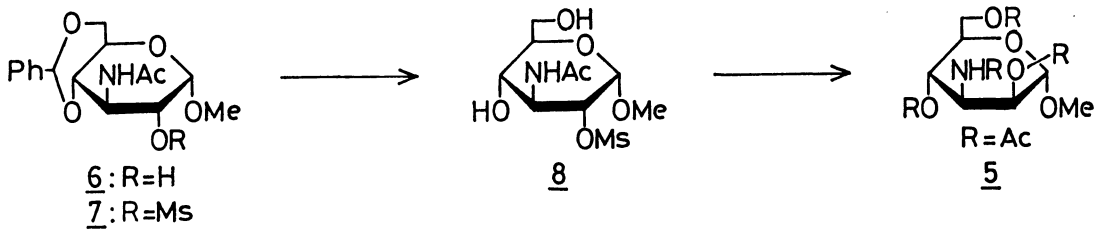


Scheme 1.

sis.[4] Soon after its isolation, the structure of 1 was established, including the absolute configuration,[3] and its total synthesis has been completed by Sharpless.[5] In this communication, we wish to report an alternative total synthesis of 1, employing methyl 3-acetamido-2,4,6-tri-O-acetyl-3-deoxy-α-manno-pyranoside (5) as a starting compound.

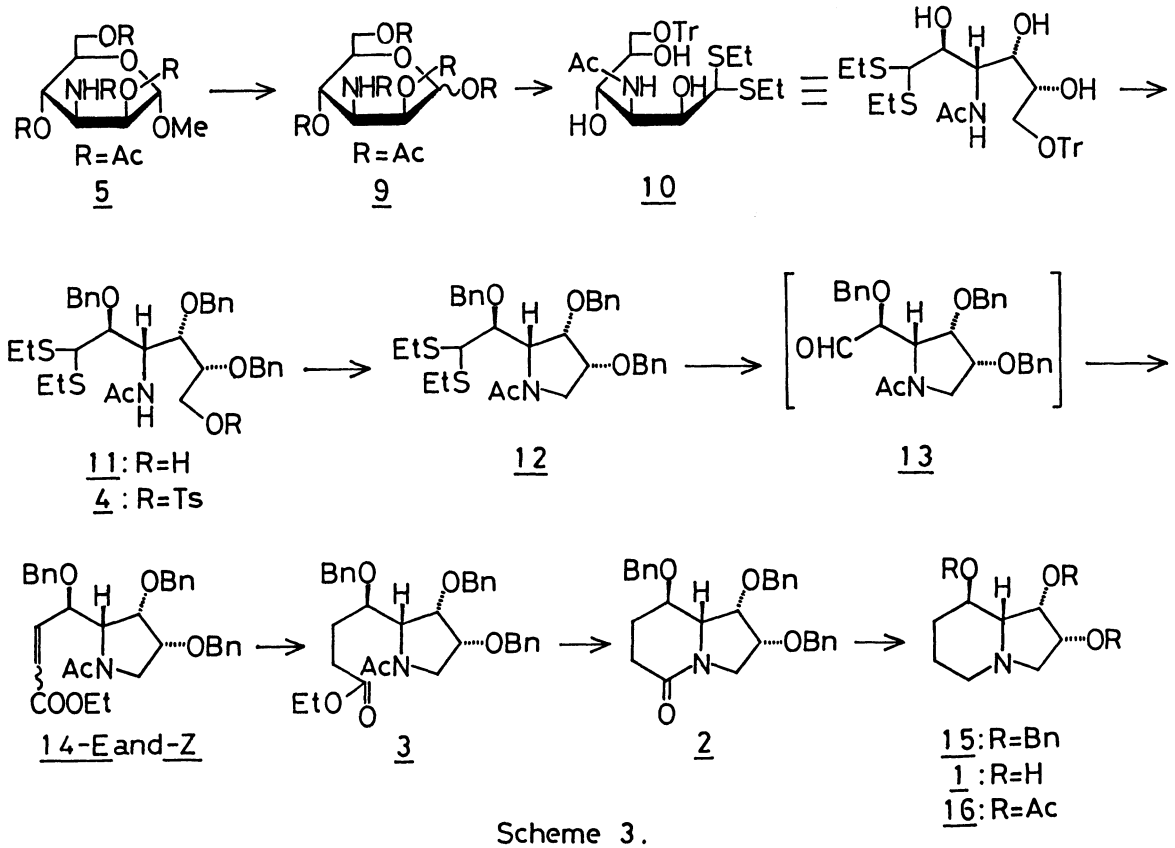
One of possible synthetic approaches to 1 would be the formation of octa-hydroindolizidine ring by the cyclization of pyrrolidine derivative (3) followed by reduction of the lactam carbonyl group as shown in the retrosynthesis (Scheme 1). Compound 4, a reasonable precursor to 3, is an acyclic form of a 3-amino-3-deoxy-D-mannose derivative which possesses all the necessary chiral carbons in 1.

Along the retrosynthetic route, the starting material 5 was prepared from methyl 3-acetamido-4,6-O-benzylidene-3-deoxy-α-D-glucopyranoside[6] (6) in a better yield of 83% (Scheme 2), compared to a yield of 16% in a literature method.[7] Mesylation of 6 in a usual manner gave the 2-O-mesyl derivative (7) in a quantitative yield. Hydrolysis of 7 in methanol containing 0.06 mol dm^{-3} HCl afforded methyl 3-acetamido-3-deoxy-2-O-mesyl-α-D-glucopyranoside (8) in 97% yield. Solvolysis of 8 in the presence of sodium acetate in aqueous 2-methoxyethanol, followed by acetylation gave 5 with the inverted configuration at C-2[8,9] in 86% yield.



Scheme 2.

Hydrolysis of 5 in 2 mol dm^{-3} HCl under reflux, followed by conventional acetylation gave 3-acetamido-1,2,4,6-tetra-O-acetyl-3-deoxy-D-mannose (9) in 98% yield as an anomeric mixture (Scheme 3). De-O-acetyaltion of 9 in methanolic sodium methoxide and subsequent treatment with ethanethiol followed by tritylation with trityl chloride in pyridine gave 3-acetamido-3-deoxy-6-O-trityl-D-mannose diethyl dithioacetal (10) in 55% yield, mp 170-172 °C; $[\alpha]_D^{28}$ -32.0° (c 1.00, $CHCl_3$). O-Benzylation of 10 with benzyl bromide in DMF in the presence of sodium hydride, followed by removal of the O-trityl group afforded the tri-O-benzyl derivative (11)



Scheme 3.

in 35% yield. Tosylation of 11 gave 4 in 77% yield, $[\alpha]_D^{23}$+5.3° (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 and 1.22 (each t, J=8 Hz, 2 x $SCH_2\underline{CH_3}$), 1.79 (s, $NCOCH_3$), 2.39 (s, $OSO_2C_6H_4\underline{CH_3}$), 2.59 and 2.60 (each q, J=8 Hz, 2 x $S\underline{CH_2}CH_3$), 7.03-7.80 (19H, 3 x $OCH_2\underline{C_6H_5}$ and $OSO_2\underline{C_6H_4}CH_3$).

An intramolecular nucleophilic displacement of 4 in 1 mol dm^{-3} NaOH under reflux afforded a pyrrolidine derivative (12) in 93% yield, which was subsequently converted to an aldehyde (13) with mercury (II) chloride and $CaCO_3$. Horner-Emmons reaction[10] of 13 with diethyl ethoxycarbonylmethylphosphonate and NaH gave a mixture of two stereoisomers which were successfully separated to give compounds 14-E and 14-Z in 75 and 2% yields, respectively. 14-E: $[\alpha]_D^{24}$+73.4° (c 1.00, $CHCl_3$); IR 1720 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.06 (dd, J=2 Hz, J=15 Hz, CH=C<u>H</u>COOEt). 14-Z: $[\alpha]_D^{22}$+87.9° (c 0.38, $CHCl_3$); IR 1740 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.26 (dd, J=2 Hz, J=11 Hz, CH=C<u>H</u>COOEt). The mixture of 14-E and 14-Z was hydrogenated over Raney nickel afforded the saturated ester 3 in 94% yield.

A lactam, 2 was prepared in 54% yield by heating 3 in aqueous ethanol contain-

ing KOH at 90 °C for 6 days. Reduction of 2 with $LiAlH_4$ in THF gave a tertiary amine (15) in 74% yield. De-O-benzylation of 15 in the presence of $Pd(OH)_2/C$ and cyclohexene[11] afforded (-)-swainsonine, 1 in 72% yield, mp 142-143 °C; $[\alpha]_D^{23}$ -81.7° (c 0.60, methanol). Lit.,[3] mp 144-145 °C; $[\alpha]_D^{20}$ -78.9° (c 1.14, methanol)[1]; $[\alpha]_D^{23}$ -87.2° (c 2.1, methanol).[3] Compound 1 was identical with an authentic sample of the natural product in the IR, ^1H NMR and MS spectra. Acetylation of 1[1] gave the tri-O-acetate (16) whose spectral data were also superimposable with those of an authentic sample.

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