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TOTAL SYNTHESIS OF SWAINSONINE[1)]

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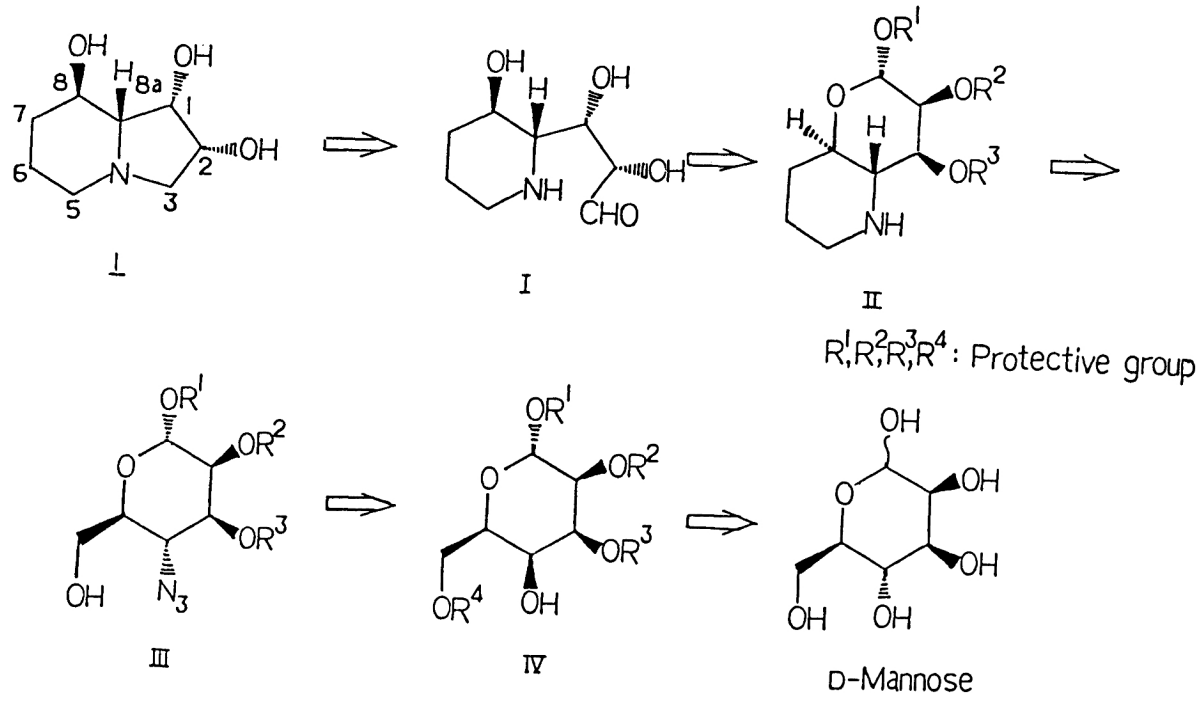
Swainsonine, a potential immunoregulator, was synthesized from D-mannose via an intermediate, methyl 4,8-imino-2,3-O-isopropylidene-4,6,7,8-tetradeoxy-α-D-manno-octopyranoside.

Recently (1S,2R,8R,8aR)-1,2,8-trihydroxyoctahydroindolizine, swainsonine(1), produced by Swainsona canescens has been isolated and determined by Colegate et al.[2)] More recently in our company, it was also isolated from the cultured broth of a fungus, Metarhizium anisopliae F3622, and was found to have the capacity to restore the depression of mitogenic responses of mouse spleen cell by immunosuppressive factor from tumor bearing mouse serum and to restore the immunosuppression induced by dexamethason, mitomycin C, or cyclophosphamide.[3)]

Thus, we became much interested in swainsonine(1) as a biological response modifier and planned its total synthesis.

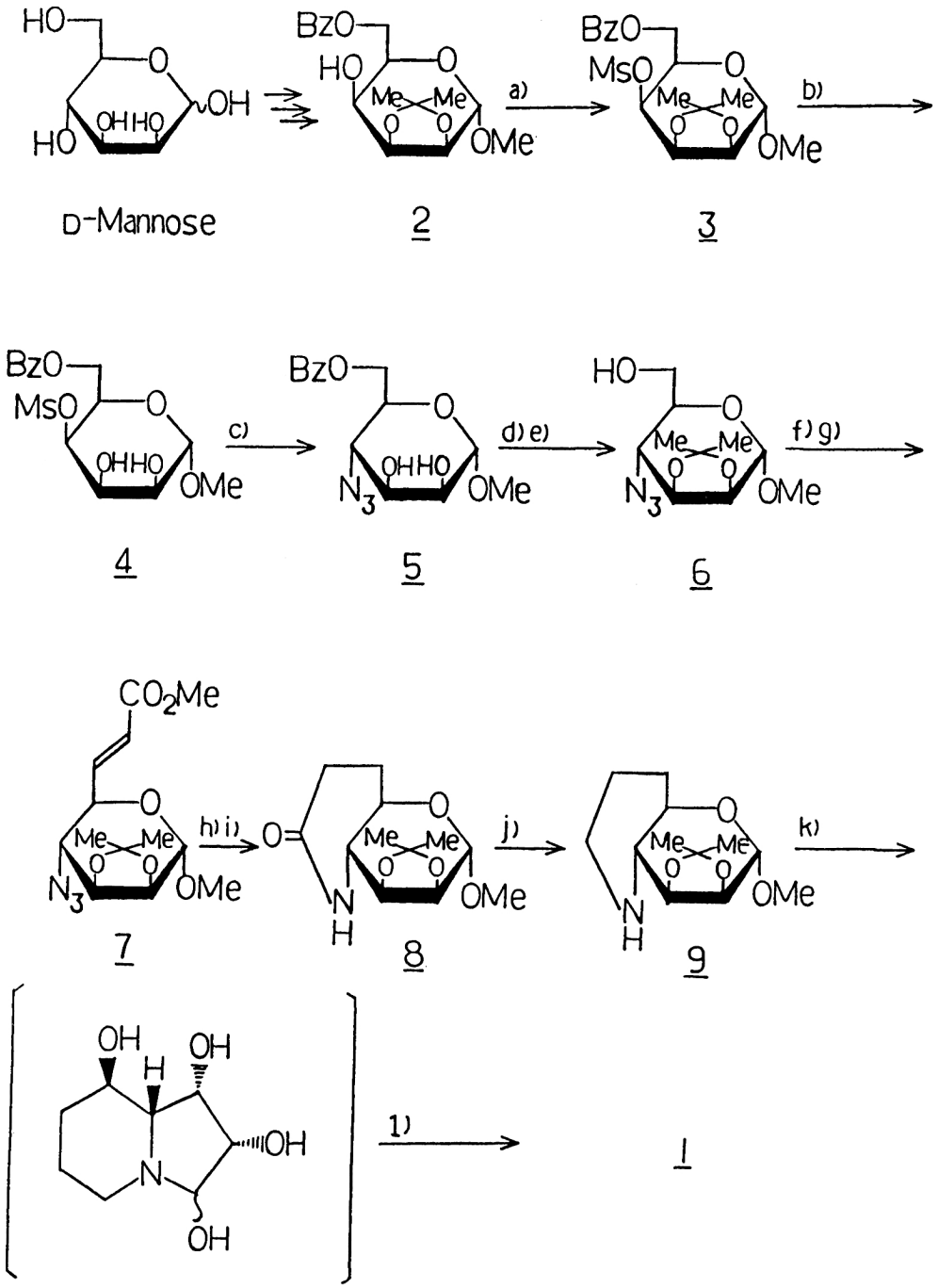
Our strategy for a total synthesis of swainsonine(1) is to utilize D-mannose as a synthon which could be led to a key intermediate, cyclic amine derivative(II), on the basis of retrosynthesis. From Scheme 1, we considered that 1 could be synthesized by introduction of an amino function at the 4-position of D-mannose, followed by elongation of a two-carbon chain at the 6-position.

Methyl 6-O-benzoyl-2,3-O-isopropylidene-α-D-talopyranoside(2) was derived from D-mannose according to the method of Evans.[4)] Mesylation of 2 in pyridine gave the corresponding 4-O-mesyl derivative(3) (mp 98-99 °C) in 88% yield. Removal of the isopropylidene group in 3 with trifluoroacetic acid at room temperature for 30 min gave methyl 6-O-benzoyl-4-O-mesyl-α-D-talopyranoside(4) (mp 90-91 °C) in 98% yield. Reaction of 4 with sodium azide in DMF at 110-115 °C for 3 h afforded methyl 4-azido-6-O-benzoyl-4-deoxy-α-D-mannopyranoside(5) (mp 96-97 °C; $[\alpha]_D^{18}$+121.2° (c 1.0, DMF); IR 2105 and 1730 cm^{-1}) in 77% yield.[5)] Protection of 5 with 2,2-dimethoxypropane, followed by alkaline hydrolysis, gave methyl 4-azido-



Scheme 1. Strategy for total synthesis of swainsonine.

4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside(6) (IR 2125 cm^{-1}; FD-MS 259 (M^+) and 244 (M^+-15)) as syrup in 98% yield. Oxidation of 6 with sulfur trioxide-pyridine complex, triethylamine, and DMSO at room temperature for 10 min gave the corresponding 6-oxo derivative (without isolation), which was treated with (methoxycarbonylmethylidene)triphenylphosphorane in THF at room temperature for 4 d to afford methyl (methyl (E)-4-azido-4,6,7-trideoxy-2,3-O-isopropylidene-α-D-manno-6-octenopyranosid)uronate(7) (IR 2100, 1715, and 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.37 and 1.57 (each s, 2 x CH_3), 3.34 (s, OCH_3), 3.75 (s, CO_2CH_3), 4.98 (s, H-1), 6.20 (dd, $J_{5,7}$=2 Hz, $J_{6,7}$=16 Hz, H-7), and 7.00 (dd, $J_{5,6}$=4 Hz, $J_{6,7}$=16 Hz, H-6); FD-MS 313 (M^+) and 298 (M^+-15)) as syrup in 56% yield. Hydrogenation of 7 in the presence of palladium black, followed by refluxing in methanol for 12 h, gave the corresponding cyclic amide derivative(8) (mp 119-120 °C; IR 1665 cm^{-1}; FD-MS 257 (M^+) and 242 (M^+-15)) in 34% yield.[6] Reaction of 8 with borane in THF under ice-cooling for 30 min gave a key intermediate, the cyclic amine(9) (mp 51-52 °C; FD-MS 243 (M^+)) in 78% yield. Demethylation of 9 was only achieved by boron trichloride. Treatment of 9 with excess boron trichloride in chloroform at -78 °C for 1.5 h and at room temperature for 16 h, followed by reduction with sodium cyanoborohydride in 50% methanol keeping the pH between 6 and 7 with 0.1 mol dm^{-3} hydrochloric acid



Scheme 2. Synthetic route for swainsonine.

at room temperature for 24 h, gave swainsonine(1)[2,7] (mp 138 °C(decomp); $[\alpha]_D^{25}$ -84.7° (c 0.53, CH_3OH); ^{13}C NMR (CD_3OD) δ 24.59, 34.12, 53.15, 63.17, 67.09, 69.88, 70.77, and 75.24) in 1.8% yield[8] by recrystallization from chloroform after silica gel column chromatography (Wakogel C-200, eluant system; $CHCl_3$-n-BuOH-EtOH-28% NH_4OH=4:4:4:1 v/v). The sample prepared above was identical with the natural product in every respect (TLC, ^1H NMR, ^{13}C NMR, Mass, ORD) and also showed the same biological activity measured by ^3H-thymidine incorporation into mouse spleen cell.

References

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4) M.E.Evans, Carbohydr. Res., 54, 105 (1977).

5) Reaction of 3 with sodium azide gave methyl 4-azido-6-O-benzoyl-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside in only 28% yield, together with two elimination products (the corresponding 3-enose derivative and the corresponding 4-enose derivative). We assumed that S_N2 reaction of 3 with azide ion could not proceed predominantly, because trioxabicyclo[4.3.0]nonane ring in 3 was rigid. Thus introduction of azide function was achieved after removal of the isopropylidene group in 3 as described in the text.

6) Many by-products were observed on TLC.

7) M.J.Schneider, F.S.Ungemach, H.P.Broquist, and T.M.Harris, Tetrahedron, 39, 29 (1983).

8) Removal of the protecting group in 9 with boron trichloride gave many spots on TLC. The resulted intermediate could be unstable in this condition.

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