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ENANTIOSPECIFIC SYNTHESIS OF SWAINSONINE, (1S, 2R, 8R, 8aR)-1,2,8-TRIHYDROXYOCTAHYDROINDOLIZINE, FROM D-MANNOSE

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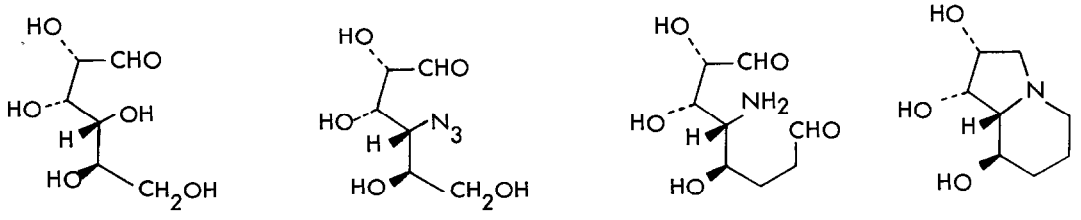
Abstract: An enantiospecific synthesis of swainsonine from D-mannose is described; the heterocyclic rings of swainsonine are constructed by two intramolecular reductive aminations caused by the catalytic hydrogenation of an azidoaldehyde with 5 equivalents of hydrogen.

Swainsonine (1), a potent and specific α-mannosidase inhibitor,[1,2] is currently the subject of many biological investigations.[3] Although the relative stereochemistry of swainsonine was determined by X-ray crystallography,[4] the absolute configuration of (1) was deduced on the basis of biosynthetic[5] and asymmetric induction[6] studies. This paper reports the unambiguous enantiospecific synthesis of swainsonine from D-mannose and confirms the absolute configuration previously ascribed. Recently, a total synthesis of castanospermine, a structurally related alkaloid, has been reported.[7]

The chiral centres in swainsonine (1) are derived from the four contiguous chiral carbon atoms in D-mannose (2) (Scheme 1). First, an azide group is introduced with overall retention of configuration to give a protected 4-azidomannose (3); subsequent two-carbon chain extension from C-6 of mannose, followed by reduction gives an equivalent of the aminodialdehyde (4) which permits the formation of the heterocyclic rings of swainsonine by two intramolecular reductive aminations.



(2) (3) (4) (1)

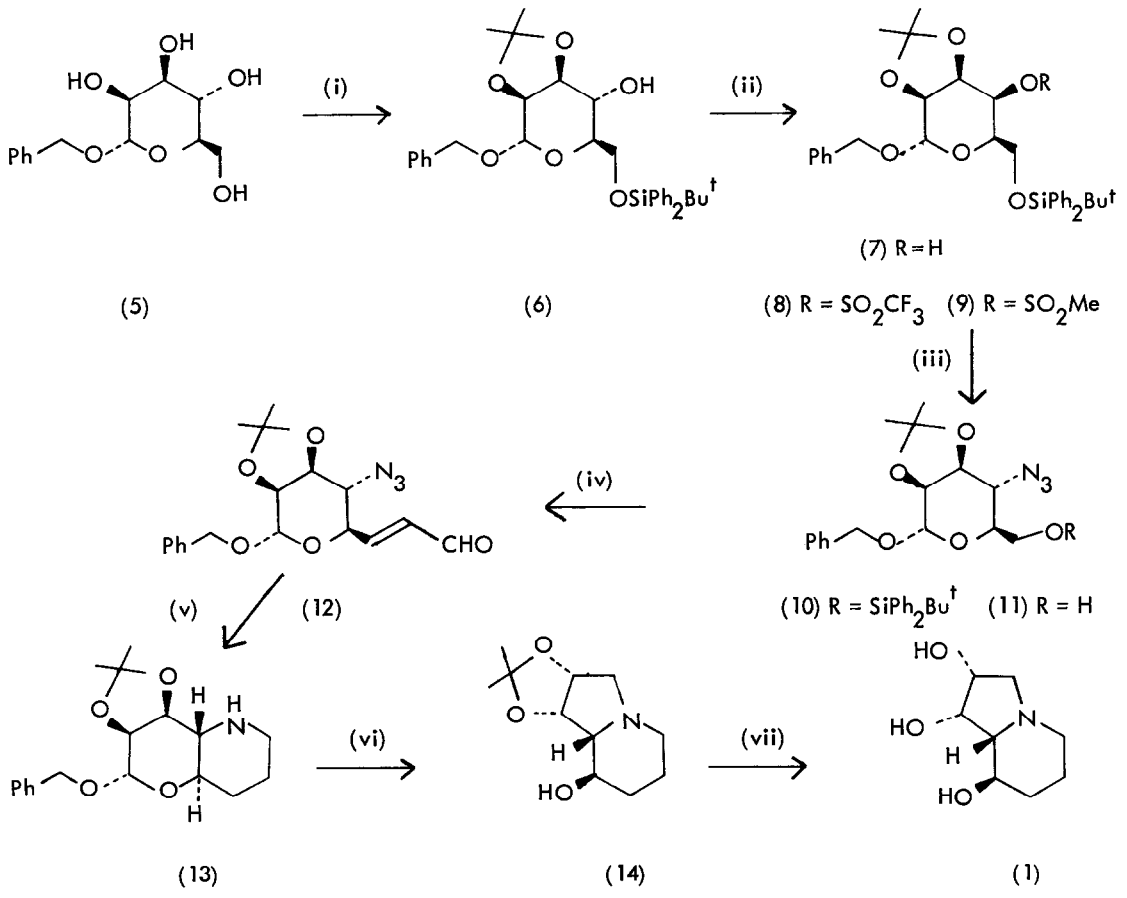
SCHEME 1

Benzyl α-D-mannopyranoside (5)[8] was treated with t-butyldiphenylsilyl chloride in the presence of

imidazole, followed by acetonation with acetone/2,2-dimethoxypropane (9:1) in the presence of a trace of camphor sulphonic acid to give (6) (86% yield)[9] in which only the C-4 hydroxyl of mannose remains unprotected. Oxidation of (6) with pyridinium chlorochromate (PCC) yielded an intermediate ketone which was reduced by sodium borohydride resulting in hydride ion attack from the least hindered face of the carbonyl to produce benzyl 6-t-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranoside (7) [88% yield from (6)]. Esterification of the alcohol (7) with trifluoromethanesulphonic anhydride/ pyridine gave the talo-triflate ester (8) which was treated with sodium azide in dimethyl formamide at room temperature to give, with a second inversion at C-4 of the sugar, the azidomannose derivative (10) [67% yield from (7)]. It is necessary to employ the triflate as the leaving group in the azide displacement reaction; attempts to displace mesylate by reaction of azide with (9) led to unsatisfactory yields of (10).[10] Removal of the protecting silyl group with fluoride ion gave benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11), m.p. 80-81° $[\alpha]_D^{20}$ + 75.0° (c, 1.7 in $CHCl_3$) [83% yield; 42% yield from benzyl α-D-mannopyranoside (5)]. Oxidation of the primary alcohol group in (11) with pyridinium chlorochromate gave an unstable intermediate aldehyde which was immediately treated with formylmethylene triphenylphosphorane,[11] $Ph_3P{=}CH.CHO$, to give the crystalline azidoaldehyde (12), m.p. 105-106°, $[\alpha]_D^{20}$ + 25.1° (c, 0.5 in $CHCl_3$) in 62% yield from (11). (Scheme 2).

Hydrogenation of the azidoenal (12) in the presence of 10% palladium on charcoal in methanol led to the formation of the secondary amine (13) in 6 hr at room temperature and pressure; this conversion requires the reduction of -CH=CH- to $-CH_2CH_2-$, the reduction of the azide group to an amine and subsequent intramolecular reductive amination of the aminoaldehyde. Removal of the anomeric benzyl group in (13) is inconveniently slow under these conditions; accordingly, after the formation of (13) is complete (as judged by tlc), the catalyst and the solvent are removed. The crude amine is then dissolved in acetic acid and hydrogenated in the presence of palladium black until all the secondary amine has been consumed; this hydrogenation causes hydrogenolysis of the benzyl group to form a lactol which is in equilibrium with an open chain aminoaldehyde which undergoes a reductive amination to form the acetonide of swainsonine (14), purified by flash chromatography, m.p. 103-106° lit.[6] 105-107°, $[\alpha]_D^{20}$ - 65.8° (c, 0.5 in MeOH), lit.[6] $[\alpha]_D^{24}$ - 75.1° (c, 1.54 in MeOH). Both the proton nmr and the mass spectral fragmentation pattern of this synthetic material are in agreement with previously published data for (14).[6] The high overall yield of the acetonide (14) [87% from azidoenal (12)] over these five consecutive hydrogenation steps is noteworthy.

The removal of the isopropylidene protecting group was accomplished by dissolving acetonide (14) in CF_3COOH - D_2O. The deprotection can then readily be monitored by nmr by observing the disappearance of the 2 methyl singlets of the isopropylidene group and the appearance of the singlet for acetone; also the multiplets for the methine hydrogens of the acetonide ring disappear to be replaced by the multiplets for the methine protons of the five ring diol at higher field. The removal of the



(i) Ph_2Bu^tSiCl/imidazole; then $Me_2CO/Me_2C(OMe)_2$, camphor sulphonic acid (ii) PCC, powdered molecular sieve, CH_2Cl_2 followed by $NaBH_4$ in EtOH (iii) $(CF_3SO_2)_2O$ (3 equiv)/pyridine in CH_2Cl_2; then NaN_3 in DMF, room temp; $Bu_4N^+F^-$ in THF (iv) PCC (2 equiv), powdered molecular sieve, CH_2Cl_2 followed by $Ph_3P{=}CH.CHO$ (2.5 equiv) (v) 10% Pd on charcoal, MeOH, H_2 room temp, 6 hr (vi) Pd black, MeCOOH, H_2, room temp, 3 days (vii) CF_3COOH (80%)-D_2O, room temp.

SCHEME 2

acetonide group is relatively slow since initial protonation of the nitrogen function in (14) reduces the rate of acid catalysed hydrolysis of the protecting group; the reaction is complete within 36 hr at room temperature. Removal of solvent followed by basification and extraction of the reaction mixture with ethyl acetate results in the formation of crude swainsonine (94% yield), m.p. and mixed m.p. with authentic sample[12] 142-144° (after sublimation), lit.[1,6] 144-145°, $[\alpha]_D^{20}$ - 67.4° (c, 0.33 in MeOH), lit.[6] $[\alpha]_D^{23}$ -87.2° (c, 2.1 in MeOH); this synthetic swainsonine gave satisfactory nmr

spectra and mass spectral fragmentation patterns in comparison with authentic swainsonine[12] and with previously published data.[1,6]

Although the yields of several steps in this sequence have yet to be optimised, this procedure should allow the ready synthesis of several gram quantities of swainsonine efficiently. Also, the unambiguous construction of the stereochemistry of the four contiguous chiral centres in this synthesis confirms that the absolute configuration previously ascribed[6] to swainsonine is correct.[13]

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