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SYNTHESIS OF THE MANNOSIDASE INHIBITORS SWAINSONINE AND 1,4-DIDEOXY- 1,4-IMINO-D-MANNITOL AND OF THE RING CONTRACTED SWAINSONINES, (1S, 2R, 7R, 7aR)-1,2,7-TRIHYDROXYPYRROLIZIDINE AND (1S, 2R, 7S, 7aR)-1,2,7-TRIHYDROXYPYRROLIZIDINE.

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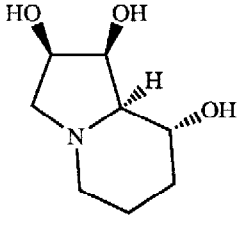
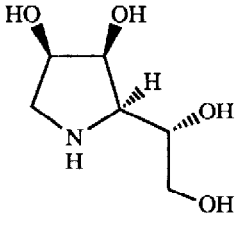
4,5-Anhydro-1-azido-1-deoxy-2,3-O-isopropylidene-D-talitol is a divergent intermediate for the efficient and practical syntheses of 1,4-dideoxy-1,4-imino-D-mannitol, swainsonine and of the ring contracted swainsonines, (1S, 2R, 7R, 7aR)-1,2,7-trihydroxypyrrolizidine and (1S, 2R, 7S, 7aR)-1,2,7-trihydroxypyrrolizidine. The effect on glycosidases of the ring contracted swainsonines is reported.

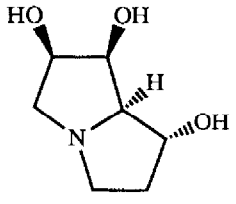
Swainsonine (1), a potent and specific inhibitor of lysosomal and some of the processing forms of α-mannosidase,[1,2] may have therapeutic value as an antimetastatic,[3] anti-tumour-proliferative,[4] or immunoregulatory agent.[5] Studies on the inhibition of human α-mannosidase by swainsonine analogues such as 1,4-dideoxy-1,4-imino-D-mannitol (DIM) (2)[6,7] have recently been reported.[8] N-Alkylation of open chain swainsonine analogues effectively removes all ability to inhibit α-mannosidase;[9] it is therefore of interest to look at the effect of variation of the size of the six-membered ring of swainsonine on the inhibition of mannosidases. There has been much interest in the synthesis of swainsonine[10] and, in particular, in procedures that could produce significant quantities of material.[11] This paper describes practical syntheses from mannose of swainsonine (1), DIM (2) and of the ring contracted swainsonines, (1S, 2R, 7R, 7aR)-1,2,7-trihydroxypyrrolizidine (3) and the 7S-epimer (4); (4) is structurally related to the pyrrolizidine alkaloid 1,7a-diepialexine (5), recently isolated from Castanospermum australe, and shown to be a powerful amyloglucosidase inhibitor.[12] The effects of the pyrrolizidines (3) and (4) on a number of glycosidases are reported.



(1)



(2)



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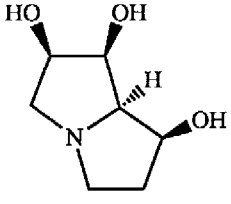
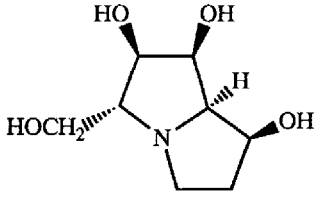


(4)



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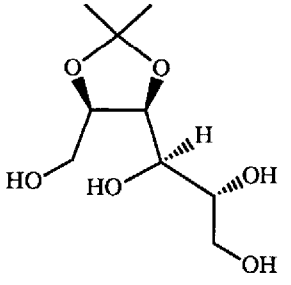
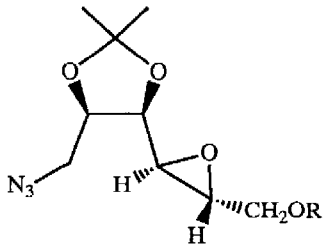
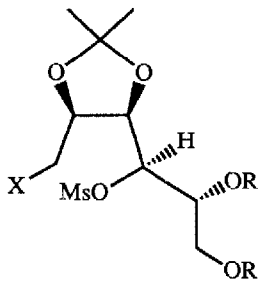


D-mannose

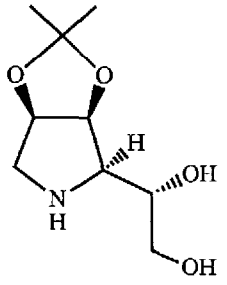
4,5-Anhydro-1-azido-1-deoxy-2,3-O-isopropylidene-D-talitol (6), derived from mannose by introduction of an azido group at C-1 and by a single inversion at C-4, is a readily available divergent intermediate for the synthesis of all the targets. The synthesis of all the synthetic targets requires the introduction of nitrogen at C-4 of mannose with overall retention, that is double inversion, of configuration. The dimesylate (10), readily available on a large scale from mannose in an overall yield of 80%,[13] undergoes selective displacement of the primary mesylate by sodium azide in *NN*-dimethylformamide:water to give the azidomesylate (11), [62% yield; 87% based on recovered (10)][14] which, on partial hydrolysis in aqueous methanol with camphorsulphonic acid, affords the diol (12), m.p. 82°-84°C, $[\alpha]_D^{20}$ +90.8° (c, 0.51 in $CHCl_3$) in 56% yield [81% based on unrecovered starting material]. Treatment of (12) with saturated methanolic barium methoxide[15] gave the azidoepoxide (6) in 95% yield. The azidoepoxide (6)[16] is moderately unstable at room temperature and the material was used immediately; (6) was fully characterised as the stable *tert*-butyldimethylsilyl (7) and *tert*-butyldiphenylsilyl (8) ethers.



(6) R = H
(7) R = TBDMS
(8) R = TBDPS
(9) R = SO_2CF_3

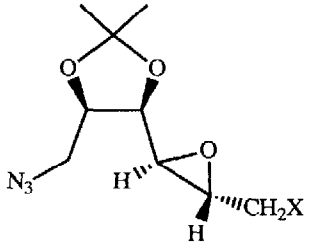


(10) X = OMs; R, R = CMe_2
(11) X = N_3; R, R = CMe_2
(12) X = N_3; R, R = H

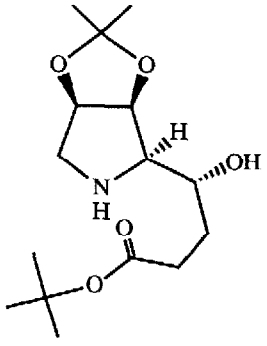


(13)

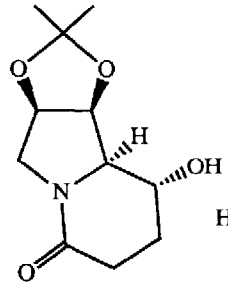
Hydrogenation of the azide (6) in 1,4-dioxane:water in the presence of palladium on carbon gave the protected pyrrolidine (13), m.p. 86°-88°C [lit.86°-88°C] in 90% yield; removal of the isopropylidene protecting group from (13) by aqueous trifluoroacetic acid, followed by conversion to the hydrochloride salt, afforded DIM (2) as the hydrochloride, m.p.149°-151°C [lit. m.p. 148°-149°C], identical to authentic material.[17]



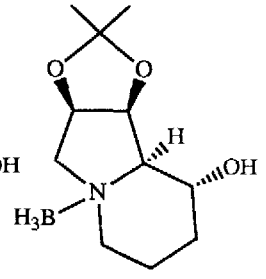
(14) X = $CH_2CO_2{}^tBu$
(15) X = CN



(16)



(17)

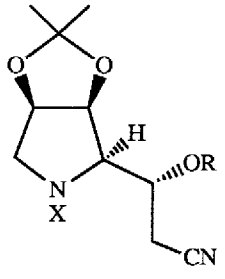


(18)

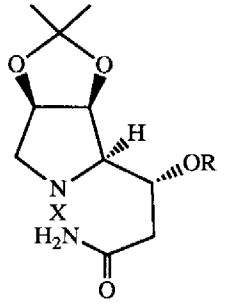
The two carbon extension for the synthesis of swainsonine was achieved by initial esterification of the primary alcohol by trifluoromethanesulphonic anhydride to give the triflate (9) which was reacted with lithium *tert*-butyl acetate in tetrahydrofuran to give the chain extended ester (14), an oil, $[\alpha]_D^{20}$ +63.5° (c, 0.98 in $CHCl_3$) in 60% overall yield from the azidomesylate (12). Hydrogenation of the azidoester (14) in ethanol with palladium on carbon as the catalyst gave the aminoester (16) (80% yield) which on heating with sodium methoxide in methanol gave the δ-lactam (17), m.p.126°-128°C [lit.[18] m.p. 125°-127°C], in 92% yield.

Reduction of the lactam (17) by borane:dimethyl sulphide gave the non-polar borane adduct (18) [70% yield] which was easily purified by flash chromatography; treatment of (18) with aqueous trifluoroacetic acid gave, after purification by ion exchange chromatography, swainsonine (1), m.p. 126°-128°C [lit. m.p. 125°-127°C], in 86% yield, identical to an authentic sample.

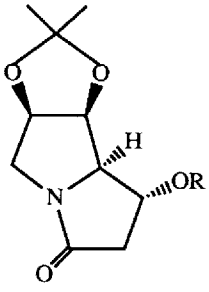
The synthesis of the ring contracted swainsonines requires a one carbon extension of the azidotriflate (9). Treatment of (9) with lithium cyanide resulted in the formation of the nitrile (15) [77% yield from (12)]; the use of lithium cyanide in this displacement is crucial.[19] Hydrogenation of (15) in ethanol with a catalyst of palladium on carbon gives (19), m.p. 92°-93°C, $[\alpha]_D^{20}$ -77.2° (c, 0.32 in $CHCl_3$) in 73% yield. Protection of the nitrogen as the benzyloxycarbonyl derivative (20), followed by partial hydrolysis of the nitrile by hydrogen peroxide in methanol in the presence of hexene gave the amide (21) which was silylated to (22) and the Z-protecting group removed to give (23), m.p.143°-144°C, $[\alpha]_D^{20}$ -55.0° (c, 0.26 in $CHCl_3$) [75% yield from (19)]. Treatment of the aminoamide (23) with a suspension of sodium hydrogen carbonate in carbon tetrachloride gave the lactam (24), m.p. 106°-109°C (92% yield) which on treatment with borane:dimethyl sulphide afforded the amine borane adduct (26) (70% yield) which with aqueous trifluoroacetic acid and purification by ion exchange chromatography gave the ring contracted swainsonine (3),[20] m.p. 150°-153°C, $[\alpha]_D^{20}$ -29.3° (c, 0.15 in MeOH) [68% yield].



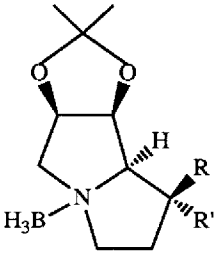
(19) X = H
(20) X = Z



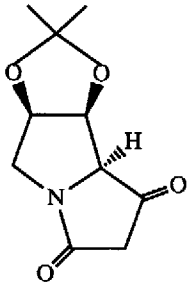
(21) R = H; X = Z
(22) R = TBDMS; X = Z
(23) R = TBDMS; X = H



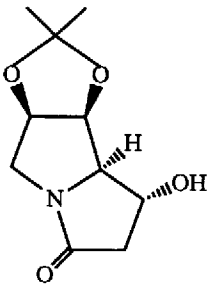
(24) R = TBDMS
(25) R = H



(26) R = H; R' = OTBDMS
(27) R = OH; R' = H



(28)



(29)

The epimeric trihydroxypyrrolizidine (4) was obtained by inversion of the free hydroxy group in (25), m.p. 148°-149°C, $[\alpha]_D^{20}$ 0° (c, 0.30 in $CHCl_3$), prepared by the removal of the silyl protecting group in (24) by fluoride (100% yield). Oxidation of (25) by pyridinium chlorochromate gave the ketone (28) which, on treatment with sodium borohydride in ethanol, cleanly gave the inverted alcohol (29), m.p. 132°-134°C, $[\alpha]_D^{20}$ -19.3° (c, 0.46 in $CHCl_3$), [94% yield from (25)]. Reduction of lactam (29) with borane:dimethyl sulphide afforded the borane adduct (27) (72% yield) which with aqueous trifluoroacetic acid and purification by ion exchange chromatography gave (4),[21] m.p. 125°-127°C, $[\alpha]_D^{20}$ -6.9° (c, 0.13 in MeOH), in 70% yield.

The effects of the ring contracted swainsonines (3) and (4) on the inhibition of 14 human liver glycosidases were studied;[22] the pyrrolizidine analogue of swainsonine (3) is a poor inhibitor of lysosomal α-mannosidase (I_{50} 1.5 x 10^{-3}M) compared with swainsonine (1) (Ki 7 x 10^{-8}M); (3) is also less effective in inhibiting the Golgi II and neutral processing mannosidases. At a concentration of 1mM, (3) also inhibited the lysosomal β-galactosidase by 69%, the broad specificity β-galactosidase/β-glucosidase moderately (25%) and α-fucosidase by 33%. The inhibition of Jack bean α-mannosidase by (3) is also very weak (Ki 1.7 x 10^{-3}M) in comparison to the inhibition by swainsonine;[23] also no significant inhibition by (3) was observed of the following glycosidases: snail β-mannosidase, yeast α-glucosidase, almond β-glucosidase, *Aspergillus niger* and green coffee bean α-galactosidases, bovine β-galactosidase, bovine kidney α-fucosidase, or bovine β-hexosaminidase.

The epimeric pyrrolizidine (4), which corresponds to 8-epi-swainsonine, does not inhibit human liver α-mannosidases but is a weak inhibitor of the broad specificity β-galactosidase/β-glucosidase (40%); in this (4) resembles the specifity of inhibition of glycosidases shown by 8-epi-swainsonine.[8] In summary, this paper reports practical syntheses of the mannosidase inhibitors swainsonine and DIM. It also demonstrates that the contraction of the piperidine ring in swainsonine to a pyrrolidine ring abolishes the potent and specific inhibition of α-mannosidases, and also decreases the inhibition of other glycosidases.[24]

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14. Satisfactory spectral data were obtained for all new compounds reported; correct CHN microanalytical data was obtained for (3), (4), (7), (8), (12), (13), (14), (17), (19), (20), (21), (22), (24), (25) and (29).
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16. For (6), ∂_C ($CDCl_3$): 110.0 (s), 76.54 and 76.44 (2d, C-2 and C-3), 60.8 (t, C-6), 56.7 and 52.3 (2d, C-4 and C-5), 50.3 (t, C-1), 27.2 and 24.7 (2q).
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20. For (3), ∂_C (D_2O): 73.74 and 73.14 (2d, C-1 and C-2), 70.9 (d, C-7), 70.6 (d, C-7a), 56.0 (d, C-3), 53.5 (t, C-5), 34.8 (t, C-6).
21. For (4), ∂_C (D_2O): 73.14 (d, C-1 and C-2), 72.8 (d, C-7), 68.0 (d, C-7a), 57.3 (d, C-3), 53.5 (t, C-5), 35.6 (t, C-6).
22. For details of assays of inhibition of human glycosidases, see references 7 and 8.
23 For details of assay of inhibition of other glycosidases, see Evans, S. V., Fellows, L. E., Shing, T. K. M., Fleet, G. W. J., *Phytochemistry*, **24**, 1953 (1985).
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