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STEREOSPECIFIC SYNTHESIS OF AN α-MANNOSIDASE INHIBITOR RELATED TO SWAINSONINE

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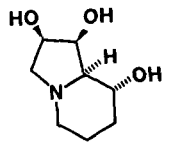
Abstract A stereospecific synthesis of pyrrolidine 2, an analog of swainsonine and an inhibitor of lysosomal α-D-mannosidase, is described.

Swainsonine (1), the neurotoxic indolizidine alkaloid found in locoweed[1] is a potent inhibitor of lysosomal and jack bean α-D-mannosidase and Golgi mannosidase II.[2,3] Administration of the alkaloid to animals affects processing of glycoproteins in the liver and results in formation of hybrid rather than complex glycoproteins.[4]

As part of our project to elucidate the mechanism of action of glycosidase enzymes[5], we have developed a stereospecific synthesis of pyrrolidine 2 and investigated its activity in lysosomal preparations.



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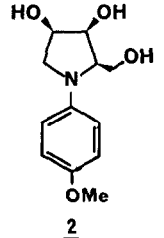
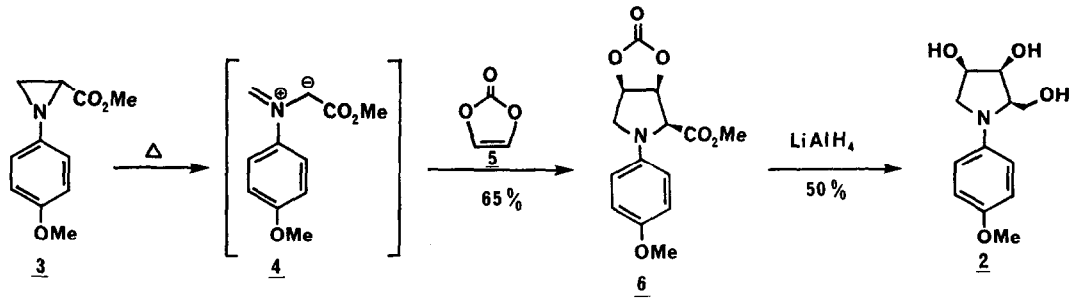


2

Heating a benzene solution of aziridine 3 and vinylene carbonate (5) at 165°C for 72 hours gave pyrrolidine carbonate 6[6] as the only cycloadduct in 65% yield. This reaction presumably proceeds by [3+2] dipolar cycloaddition of azomethine ylid 4 and 5.[7] Simultaneous reduction of the carbonate and ester moieties with $LiAlH_4$ gave triol 2 (50%).[8] Using this procedure, it is possible to secure multigram quantities of 2 from readily available materials.

Preliminary studies have shown that racemic pyrrolidine 2 specifically inhibits the α-D-mannosidase activity in an extract of purified liver lysosomes.[9] At a concentration of 8mM, pyrrolidine 2 produced 50% inhibition of the mannosidase activity[10] while the activities of β-D-mannosidase, β-D-galactosidase, N-acetyl-β-D-glucosaminidase and α-L-fucosidase were unaffected.



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Reference and Notes.

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5. Nojirimycin, deoxynojirimycin, castanospermine, and 1,5-dideoxy-1,5-imino-5-mannitol have also been shown to be specific inhibitors of various glycosidase enzymes.
6. Pyrrolidine 6: m.p. 140-1°C; IR(KBr)1815(s),1730(s)cm^{-1}; ^{1}H NMR(acetone-d$_6$) δ6.77(m,4H),5.68(t,J=7.0,1H),5.50(ddd,J=7.0,5.0,1.0,1H),4.45(d,J=7.0,1H), 4.00 (dd,J=11.5,1.0,1H),3.71(s,6H),3.50(dd,J=11.5,5.0,1.0,1H); mass spectrum, m/z (rel. int.)293(22),234(100). Anal. Calcd. for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found:C, 57.42; H, 5.21; N, 4.75.
7. For additional examples of azomethine ylid cycloadditions see DeShong, P.; Kell, D. A.; Sidler, D. R. J. Org. Chem. 1985, 50, in press, and references cited therein.
8. Triol 2: m.p. 126-7°C; IR(KBr)3400-3150(BR); ^{1}H NMR(acetone-d$_6$)δ6.70(m,4H), 4.40(m,1H),3.97(m,2H),3.77(m,2H),3.68(s,3H),3.40(dd,J=10.5,1.0,1H),3.29 (dd,J=10.5,4.5,1H),2.92(s,3H); mass spectrum, m/z (rel. int.)239(14),208 (100).
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10. IC$_{50}$ for swainsonine is 8μM. Further results in the inhibition of α-D-mannosidase systems by swainsonine analog 2 and related substances will be reported elsewhere.

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