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A SIMPLE, STEREOSPECIFIC SYNTHESIS OF (+)-MUSCARINE

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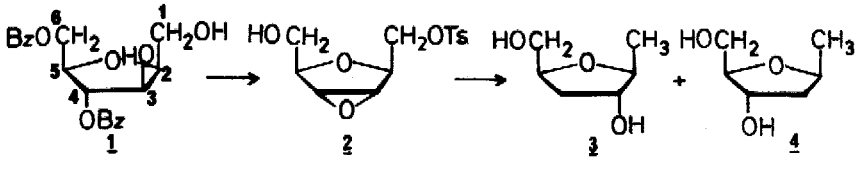
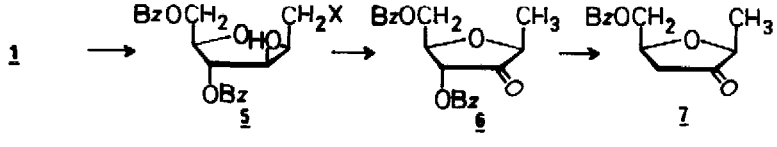
A high-yielding stereospecific synthesis of the toxic principle (+)-muscarine from D-mannitol via 2,5-anhydro-D-glucitol is described.

The toxic principle (+)-muscarine, isolated from the mushroom Amanita muscaria, has generated much interest due to its specific cholinomimetic activity. [1] Syntheses of this alkaloid, however, have involved many steps with low product yields. [2] We wish to report a simple, high-yielding and stereospecific synthesis from the inexpensive chiral starting material D-mannitol.

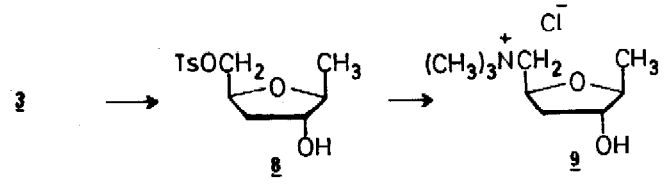
Acid catalysed dehydration of D-mannitol gives 2,5-anhydro-D-glucitol [3] readily isolated as the 1,3-O-isopropylidene derivative, m.p. 127-129°, of its dibenzoate (1). [4,5] Reaction of (1) with excess of tosyl chloride in



pyridine afforded a ditosylate, m.p. 65-69°, which with sodium methoxide (1.1 mol) in methanol gave the epoxide (2), m.p. 60-61°, (70% from 1). Reduction of (2) with sodium bis-(2-methoxyethoxy)-aluminium hydride(Red-al) in THF was highly regioselective giving a 12:1 mixture of the diols (3) and (4) quantitatively. Reduction using LAH gave a 3:1 mixture. The regioselectivity is attributed to intramolecular hydride transfer in an alkoxyalumino hydride intermediate.



The structure of the major isomer (3) was confirmed by an alternative synthesis in which (1) was converted by Ph_3P/CCl_4 in acetonitrile to (5;X=Cl) m.p. 104-105°, whence reduction with tributyltin hydride and AIBN in benzene gave (5;X=H), m.p.66-68° (90% overall). Pyridinium chlorochromate oxidation in benzene[6] gave the ketone (6) which was reduced to the deoxyketone (7) with $Cr(II)Cl_2$ in aqueous acetone.[7] Sodium borohydride reduction then debenzoylation gave (3) together with the epimeric alcohol in a ration of 2:3.



Monotosylation of the diol mixture (3) and (4), then chromatographic resolution gave (8) in 65% yield from (2). Treatment of (8) with trimethylamine in anhydrous MeOH followed by ion-exchange afforded (+)-muscarine chloride (9)(75%), m.p. 182-183° (lit.,[1b] 181-182°) and $[\alpha]_D^{25}$ + 8.3° (c,2.75 EtOH) (lit.,[1b] + 8.1°).

We note that the above intermediates are well suited to the synthesis of analogues of the muscarine system. The potential of the anhydro-D-glucitol system as an intermediate in C-nucleoside synthesis has been noted;[5] we have already used (1) in a synthesis of β-D-2'-deoxyshowdomycin.[8]

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References and Footnotes

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