The Stereospecific Synthesis of *S*(−)Piperidin-3-ol

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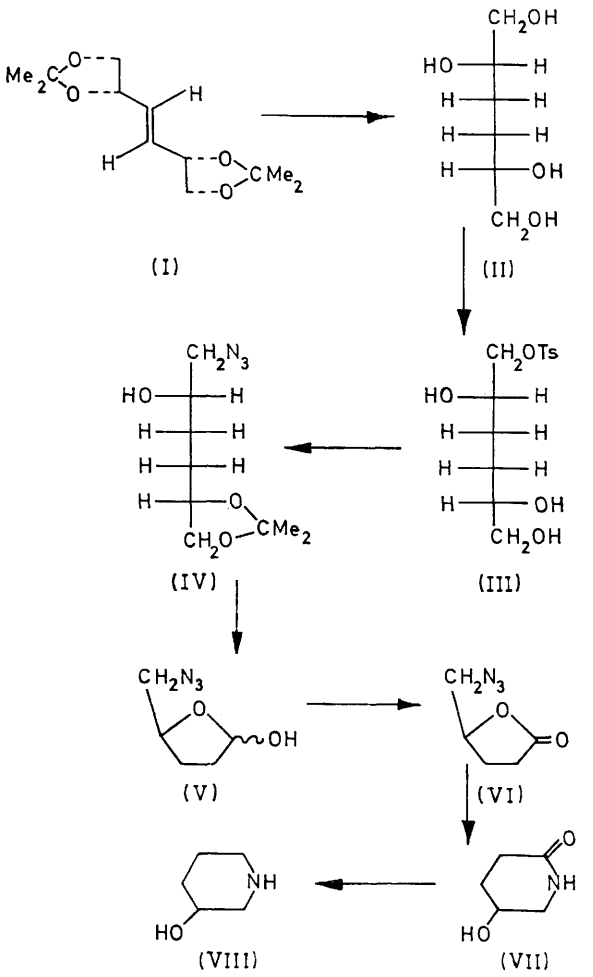
Summary The stereospecific synthesis has been achieved, starting from mannitol.

As part of a study for the stereospecific synthesis of pharmacologically and biochemically important chiral compounds from readily available carbohydrates, we have recently reported the syntheses and configurational assignments of some chiral hydroxyacetic acids.[1] We now report the stereospecific synthesis of *S*(−)-piperidin-3-ol from a carbohydrate precursor.

Mannitol was converted *via* its 1,2 : 5,6-di-*O*-isopropylidene-3,4-di-*O*-methanesulphonyl derivative into *trans*-3,4-didehydro-3,4-dideoxy-1,2 : 5,6-di-*O*-isopropylidene-D-*threo*-hexitol[2] (I). Sequential hydrogenation and hydrolysis of (I) yielded hexane 1,2(*S*),5(*S*),6-tetraol {(II), m.p. 84° (from ethanol–ethyl acetate), $[\alpha]_D$ − 25° (*c*. 2·5 in $CHCl_3$)}. Dropwise addition of an equimolar quantity of toluene-*p*-sulphonyl chloride in pyridine at 0° to the tetraol (II) in pyridine at 0° yielded principally the 1-*O*-toluene-*p*-sulphonate (III). Crude (III) was treated in sequence with acetone–$CuSO_4$ and sodium azide in *NN*-dimethylformamide to yield the azide {(IV), $[\alpha]_D$ − 7° (*c* 2 in $CHCl_3$)} which was purified by chromatography over silica [ether–light petroleum (40—60°) 1 : 1]. Hydrolysis and periodate oxidation of (IV) gave the furanoid derivative {(V), R_F† 0·4, ether–light petroleum 1 : 1} as a mixture of anomers (shown by n.m.r.) which were not further characterised but were oxidised directly with chromium trioxide in pyridine.[3] Repeated treatments were necessary to effect complete conversion of (V) into 5(*S*)-5-azidomethyl-γ-butyrolactone {(VI), (R_F† 0·15, ether–light petroleum 1 : 1) $[\alpha]_D$ + 56° (*c* 2 in $CHCl_3$)}. Catalytic hydrogenation[3] of the azidolactone (VI) with 10% palladium on charcoal yielded 5(*S*)-hydroxypiperid-2-one {(VII) m.p. 125—127° (from methanol)} which crystallised from methanol on storing for two to three days at 0°. In water (VII) (0·1 g.) had no measurable rotation (Hilger–Watts Mk. III Polarimeter).

Lithium aluminium hydride reduction of (VII) in boiling dioxan yielded (*S*)-piperidin-3-ol {(VIII), $[\alpha]_D$ − 7·5 (*c* 2 in MeOH)} which crystallised slowly on storage and was spectroscopically indistinguishable from authentic material.



To our knowledge this configurational assignment for *S*(−)-piperidin-3-ol, is the first reported for a cyclic imino-alcohol.

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† R_F values quoted for chromatoplates of Merk Silica Gel G.

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[3] S. Hanessian and T. H. Haskell, *J. Heterocyclic Chem.*, 1964, **1**, 55; H. Paulsen, *Angew. Chem. Internat. Edn.*, 1966, **5**, 495.