A Short and Practical Synthesis of (2*S*,5*S*)-Bishydroxymethyl-(3*R*,4*R*)-bishydroxypyrrolidine

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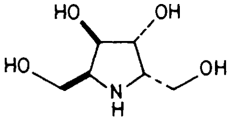
D-Mannitol has been converted by five sequential reactions (benzylidenation, trifluoromethanesulphonation, hydrazinolysis, hydrogenolysis, and deacetalisation) into (2*S*,5*S*)-bishydroxymethyl-(3*R*,4*R*)-bishydroxypyrrolidine.

Recently, both natural[1] and synthetic[2] polyhydroxylated pyrrolidines have displayed considerable potential as glycosidase inhibitors.[3] The asymmetric inducing properties of hydroxylated pyrrolidine derivatives as chiral auxiliaries in alkylation,[4] acylation,[5] and aldolisation[6] have also been demonstrated. The existing syntheses[2,7] of polyhydroxylated pyrrolidines from sugars constructed the nitrogen–carbon bonds of the heterocyclic ring individually, and thus entailed many protection and deprotection steps. Now, we report a short and efficient synthesis of (2*S*,5*S*)-bishydroxymethyl-(3*R*,4*R*)-bishydroxypyrrolidine (2,5-dideoxy-2,5-imino-L-iditol) (**1**) in which the pyrrolidine framework is formed in one transformation and chromatography is not required.

Benzylidenation of D-mannitol (**2**) afforded the highly crystalline 1,3 : 4,6-diacetal (**3**)[8] (Scheme 1) which was converted into the bistrifluoromethanesulphonate (**4**),† m.p. 74—75 °C; $[\alpha]_D^{20}$ −23.1° (*c* 1.3, $CHCl_3$). Nucleophilic displacement of (**4**) with hydrazine produced the pyrrolidine framework (**5**), m.p. 136—138 °C; $[\alpha]_D^{20}$ + 58.2° (*c* 0.96, $CHCl_3$). Formation of the alternative six-membered heterocycle was not observed since the rate of ring-closure is faster for five-membered rings.[9] Complete deblocking of (**5**) by catalytic hydrogenolysis proved troublesome, but (**5**) could be partially hydrogenolysed over Raney-nickel[10] to give pyrroli-



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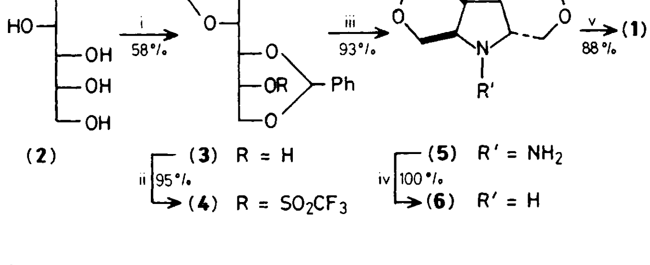

Scheme 1. *Reagents:* i, PhCHO, $HCONMe_2$, H_2SO_4; ii, $(CF_3SO_2)_2O$, tetrahydrofuran (THF), pyridine, −5 °C; iii, anhydrous hydrazine, THF; iv, Raney-nickel, H_2, THF–ethanol; v, aqueous trifluoroacetic acid.

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† All new compounds gave satisfactory analytical and spectral data.

dine (**6**)‡[11] in quantitative yield, m.p. 121—122 °C; $[\alpha]_D^{20}$ + 15.0° (*c* 0.5, $CHCl_3$). Deacetalisation of this material furnished the hydroxylated alkaloid (**1**), m.p. 161—162 °C, $[\alpha]_D^{20}$ + 14.3° (*c* 0.93, H_2O) [78% yield from (**3**)].

It is noteworthy that the easy accessibility of (**5**) and (**6**) makes them attractive chiral auxiliaries with C_2 symmetry in asymmetric synthesis.

I thank Professor J. K. Sutherland for valuable discussion.

Received, 19th September 1986; Com. 1344

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‡ Reaction of bistrifluoromethanesulphonate (**4**) with ammonia provided (**6**) directly but in a lower yield (68%).