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Enantiospecific Synthesis of D-Mannono-δ-lactam from Vitamin C

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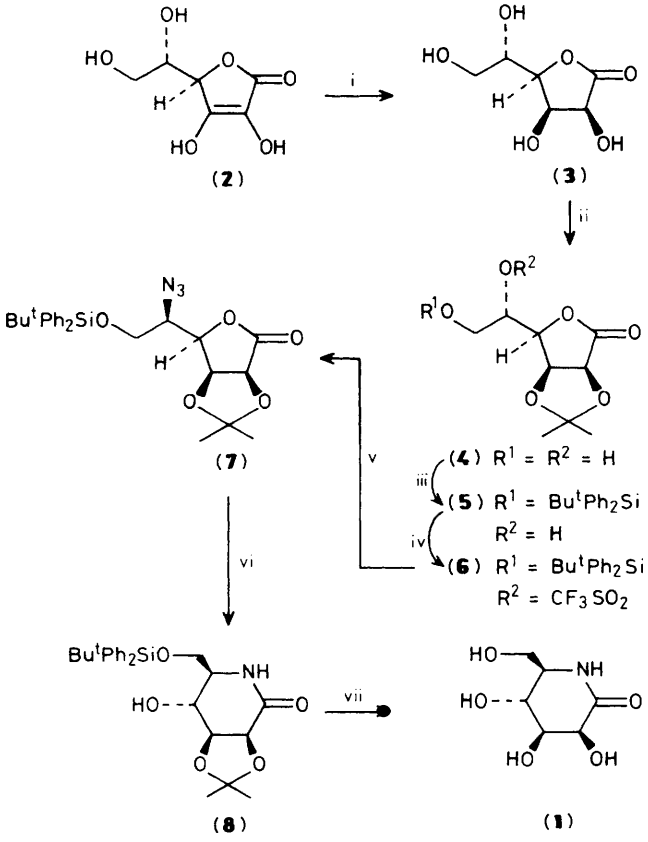
An eight-step synthesis of the glycosidase inhibitor D-mannono-δ-lactam from vitamin C is described.

Very recently, the potential of polyhydroxylated δ-lactams as a new class of glycosidase inhibitors has been indicated.[1] D-Mannono-δ-lactam (**1**), previously formed by microbial oxidation of nojirimycin B, is a potent inhibitor of rat epididymal α-mannosidase and of apricot β-glucosidase.[2] This communication reports the first enantiospecific synthesis of (**1**) from a non-carbohydrate precursor, vitamin C (**2**).



Scheme 1. *Reagents:* i, Pd, H_2, H_2O (100%); ii, Me_2CO/HCl then aq. AcOH (68%); iii, Bu^tPh_2SiCl, pyridine (95%); iv, $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine (92%); v, $Bu_4^nNN_3$, tetrahydrofuran (76%); vi, H_2, $Pd(OH)_2$, EtOAc (88%); vii, aq. CF_3CO_2H (85%).

The strategy involves a stereoselective hydrogenation from the less hindered side of the enediol (**2**) to secure the chirality of the resultant C-2 and C-3 hydroxy groups and introduction of nitrogen with inversion of configuration at C-5. Thus hydrogenation of (**2**) gave stereospecifically the saturated lactone (**3**),[3] which was bis-acetonated and then partially hydrolysed to the diol (**4**),† m.p. 130—132 °C (Scheme 1). The primary hydroxy group in (**4**) was protected by *O*-silylation to give (**5**), $[\alpha]_D^{20}$ + 61.1° (*c* 1.4 in $CHCl_3$), which was subsequently esterified to give the trifluoromethanesulphonate (**6**). A nucleophilic displacement reaction of (**6**) with tetrabutylammonium azide afforded the azido lactone (**7**), m.p. 97—98 °C; $[\alpha]_D^{20}$ +6.5° (*c* 1.4 in $CHCl_3$), which was hydrogenolysed to form the protected lactam (**8**), $[\alpha]_D^{22}$ +35.8° (*c* 0.6 in $CHCl_3$). Hydrolysis then furnished D-mannono-δ-lactam (**1**), m.p. 170—172 °C; $[\alpha]_D^{22}$ +2.0° (*c* 0.8 in water) {lit.[2] m.p. 169—170 °C, $[\alpha]_D^{20}$ +1.6° (*c* 1.0 in water)}.

Synthetic applications of vitamin C, enhanced by its cheapness and availability, should attract more attention from organic chemists.

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† All new compounds gave satisfactory analytical and spectral data.