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Synthesis of 2*S*-Hydroxymethyl-3*R*, 4*R*-dihydroxypyrrolidine

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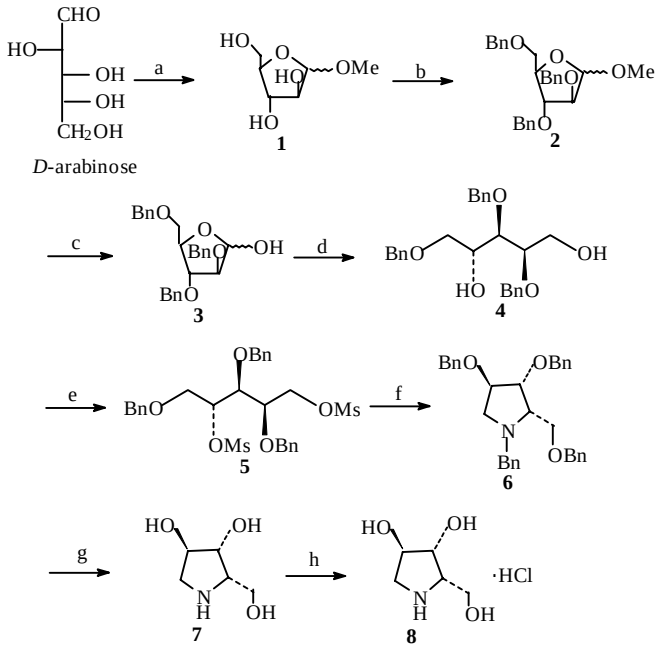
Abstract: The sythesis of 2*S*-hydroxymethyl-3*R*, 4*R*-dihydroxypyrrolidine from *D*-arabinose was described in this paper.

Keywords: Polydroxylated pyrrolidine, 2*S*-hydroxymethyl-3*R*, 4*R*-dihydroxypyrrolidine, *D*-arabinose.

Many polyhydroxylated alkaloids exhibit glycosidase inhibitory activities[1]. Polyhyroxylated pyrrolidine is a type of important alkaloidal glycosidase inhibitors[2]. For example, 2*R*-hydroxymethyl-3*R*, 4*R*-dihydroxypyrrolidine (1,4 – dideoxy –1,4 –imino – *D* – arabinitol), a naturally occurring polyhydroxylated pyrrolidine[3], is a potent inhibitor of α - glucosidase[4]. Prompted by interests in the remarkable physiological effects, some polyhydroxylated pyrrolidine and their derivatives have been synthesized[4,5]. In this paper, we describe the synthesis of 2*S*-hydroxymethyl-3*R*, 4*R*-dihydroxypyrrolidine from *D*–arabinose (**Scheme**).

Scheme



a) H_2SO_4/CH_3OH, anhydrous $CaSO_4$;
b) BnBr, NaH, n-Bu_4NI in DMF and THF, r.t;
c) CH_3COOH/6Mol/LHCl, 65°C;
d) $NaBH_4$ in ethenol;
e) CH_3SO_2Cl, Et_3N, CH_2Cl_2;
f) $BnNH_2$ in toluene, reflux;
g) H_2, 10%Pd-C, CH_3COOH, 40psi, 50°C;
h) HCl, CH_3OH.

As shown in **Scheme**, *D* – arabinose was converted to 2, 3, 5 – tri – *O* – benzylarabinofuranose **3** by three steps (overall yield 32%). Reduction of **3** with sodium borohydride in ethanol gave 2, 3, 5 – tri – *O* – benzyl arabinol **4** (93% yield), followed by esterification of the resulting diol with mesyl chloride in methylene in the presence of Et_3N to form the dimesylate **5** (93% yield). Then, the dimesylate reacted with benzylamine in toluene to give the protected five-numbered homoazasugar **6** (79% yield). Finally, the benzyl groups were removed by catalytic hydrogenolysis on 10% palladium-carbon to give the title compound **7**[6] in almost quantitative yield. Its hydrochloride **8** is a white solide with m.p. 121-123°C. Further synthetic and pharmacological studies of the title compound and its derivatives are in progress.

Acknowledgments

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6. Compound **7**: $[\alpha]_D$ +4.6 (*c* 0.54, H_2O); EIMS(m/z) 134 (6%, M+1), 102 (100%, M-CH_2OH); ^{1}H NMR (500MHz, D_2O) δ 2.81 (d, 1H, H-5a), 3.33-3.39 (m, 2H, H-5b and H-2), 3.74 (q, 1H, H-6a), 3.86 (q, 1H, H-6b), 4.18 (br, 1H, H-3), 4.24 (br, 1H, H-4); ^{13}C NMR (125Hz, D_2O) δ 49.0 (C-5), 58.2 (C-6), 59.1 (C-2), 75.0 (C-4), 75.4 (C-3).

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