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SYNTHESIS OF (2*S*,5*S*)-BISHYDROXYMETHYL-(3*R*,4*R*)-BISHYDROXYPYRROLIDINE FROM D-MANNITOL

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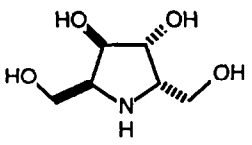
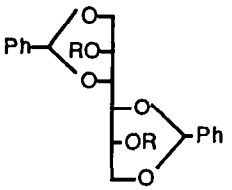
Abstract—A short, efficient, and practical synthesis of (2*S*,5*S*)-bishydroxymethyl-(3*R*,4*R*)-bishydroxypyrrolidine from D-mannitol involving five sequential reactions (benzylidenation, trifluoromethanesulphonation, hydrazinolysis, hydrogenolysis, and deacetalisation) is described.

Both natural[1] and synthetic[2] polyhydroxylated pyrrolidines have already shown great promise as a class of potent and specific glycosidase inhibitors.[3] Recently, a dihydroxymethyldihydroxypyrrolidine has displayed potential as an antiviral agent since its inhibition of virus replication has been demonstrated.[4] There is also considerable interest in using hydroxylated pyrrolidine derivatives[5] as chiral auxiliaries in asymmetric synthesis, e.g. the asymmetric inducing properties of trans-2,5-bis(methoxymethoxymethyl)pyrrolidine (with C_2 symmetry) in alkylation,[6] acylation,[7] aldolisation,[8] and Wittig rearrangement[9] have been reported; and (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine (*S*AMP and *R*AMP) have been shown to be efficient chiral auxiliaries for the asymmetric syntheses of carbonyl compounds and primary amines.[10]

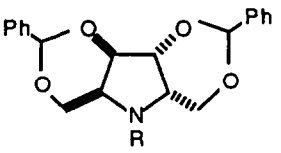
Earlier syntheses[2,11] of polyhydroxylated pyrrolidines from sugars constructed the nitrogen-carbon bonds of the heterocyclic ring individually, and thus entailed many protection and deprotection steps. This paper describes, with minimum protecting group chemistry, a short, efficient, and practical 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 synthetic operation and chromatography is not required. Since the appearance of the preliminary account[12] of this work, it is pleasing to see that recent syntheses[13] of hydroxylated pyrrolidines have adopted the strategy of heterocyclic ring formation in one step.



(1)



(2) R = H
(3) R = SO_2CF_3



(4) R = NH_2
(5) R = H

The hydroxylated alkaloid (1) was prepared in five steps from D-mannitol in an overall yield of 45%. Thus acetalisation of D-mannitol with benzaldehyde as described previously[14] gave the highly crystalline 1,3:4,6-di-*O*-benzylidene-D-mannitol (2) (58%) which was esterified with trifluoromethanesulphonic (triflic) anhydride in the presence of pyridine to form the bisester (3) in 95% yield. Nucleophilic substitution of (3) with anhydrous hydrazine afforded cleanly the pyrrolidine framework (4) in 93% yield. Formation of the alternative six-membered heterocycle was not observed since the rate of ring closure is faster for five-membered rings.[15] Total deprotection of (4) by catalytic hydrogenolysis, a conversion which would complete the synthesis of (1), proved troublesome. However, (4) could be partially hydrogenolysed smoothly over Raney-nickel[16] to give pyrrolidine (5)[17] in quantitative yield. Compound (5) could also be obtained directly from the reaction of the bisester (3) with ammonia, but in a lower yield of 68%. The hydrazine is a more powerful nucleophile than ammonia, attributable to the alpha effect.[18] Finally, the acetal groups in (5) were hydrolysed with aqueous trifluoroacetic acid to the hydroxylated alkaloid (1) in 88% yield. The physical properties of (1) are different to those of the known (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*R*)-dihydroxypyrrolidine[11] and the ^{1}H n.m.r. spectrum of (1) exhibited simplified signals ascribable to the symmetry element (C_2) of the molecule. These data confirm that the cyclisation to the pyrrolidine framework (4) proceeded with inversion of configuration at C-2 and at C-5 of the bisester (3).

The potential of the easily accessible hydrazine derivative (4) and pyrrolidine (5) as chiral auxiliaries with C_2 symmetry in asymmetric synthesis is currently under investigation.

Experimental

M.p.s were recorded on a Kofler block. ^{1}H N.m.r. spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated; all compounds (1)—(5) have C_2 symmetry, hence 1-, 2-, and 3-H (sugar-numbering) are magnetically equivalent to 4-, 5-, and 6-H respectively. Mass spectra were recorded on a Kratos MS25 instrument. Optical rotations were measured on an AA-100 polarimeter using chloroform as solvent unless otherwise stated. T.l.c. was performed on glass plates precoated with Merck silica $60F_{254}$, and compounds were visualised with a spray of 5% v/v

sulphuric acid in ethanol and subsequent heating. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under dry nitrogen. Pyridine was distilled from anhydrous barium oxide.

1,3:4,6-Di-O-*benzylidene-2,5-di*-O-*trifluoromethylsulphonyl*-D-*mannitol* (3). A solution of the diol (2) (780 mg, 2.2 mmol) in dry THF (17 ml) containing dry pyridine (2 ml) was cooled to -5 °C and stirred while triflic anhydride (0.96 ml, 2.6 equiv.) was added dropwise during 10 min. The mixture was stirred for a further 1.5 h at O °C, quenched with cold aqueous potassium orthophosphate (1 M, 40 ml), and extracted with chloroform (3 X 20 ml). The combined extracts were dried (Na_2SO_4) and filtered through a pad of silica topped with Celite. Concentration of the filtrate gave a syrup which was co-distilled with toluene to remove the residual pyridine, and afforded the *triflate* (3) (1.3 g, 95%) as a solid, m.p. 74—75 °C; $[\alpha]_D^{20}$ -23.1° (*c* 1.3); R_F 0.7 [diethyl ether-hexane (1:1 v/v)]; δ 3.97 (2 H, t, *J* 10.5 Hz, 1'- and 6'-H), 4.18 (2H, d, *J* 9.1 Hz, 3- and 4-H), 4.56 (2H, dd, *J* 5.4 and 10.5 Hz, 1- and 6-H), 5.31 (2H, ddd, *J* 5.4, 9.1 and 10.5 Hz, 2- and 5-H), 5.54 (2H, s, PhC*H*),7.38—7.49 (10H, m, Ph) (Found: C, 42.9; H, 3.3; S, 10.8. $C_{22}H_{20}F_6O_{10}S_2$ requires C, 42.5; H, 3.2; S, 10.3%).

N-*Amino-1,3:4,6-Di*-O-*benzylidene-2,5-dideoxy-2,5-imino*-L-*iditol* (4). A solution of the triflate (3) (3.12 g, 5 mmol) in dry THF (40 ml) containing anhydrous hydrazine (10 ml) was stirred at room temperature for 20 h. Removal of solvent gave a syrup which was dissolved in ethyl acetate (200 ml). The solution was washed with cold aqueous sodium hydroxide (1 M, 3 X), dried (Na_2CO_3), filtered through a pad of silica, and the filtrate concentrated. Trituration of the residue with diethyl ether afforded the *title compound* (4) (1.65g, 93%) as colourless plates, m.p. 136—138 °C; $[\alpha]_D^{20}$ +58.2° (*c* 0.96); R_F 0.5 (ethyl acetate); δ 3.42 (2H, br s, 2- and 5-H), 4.17 (2H, dd, *J* 2.3 and 12.6 Hz, 1'- and 6'-H), 4.43 (2H, d, *J* 2.5 Hz, 3- and 4-H), 4.63 (2H, d, *J* 12.6 Hz, 1- and 6-H), 5.54 (2H, s, PhC*H*), 7.35—7.48(10H, m, Ph); *m/z* (EI) 354 (10%, M^+) (Found: C, 67.5; H, 6.2; N, 8.1. $C_{20}H_{22}N_2O_4$ requires C, 67.8; H, 6.2; N, 7.9%).

1,3:4,6-Di-O-*benzylidene-2,5-dideoxy-2,5-imino*-L-*iditol* (5). A solution of the hyrazine derivative (4) (785 mg, 2.2 mmol) in THF/ethanol (15 ml, 1:1 v/v) was hydrogenated over Raney-nickel[16] at room temperature and atmospheric pressure for 24 h. The mixture was filtered through Celite and the filtrate concentrated to give a quantitative yield of the *pyrrolidine* (5), m.p. 121—122 °C (from diethyl ether); $[\alpha]_D^{20}$ +15° (*c* 0.5); R_F 0.45 (ethyl acetate); δ 2.71 (1H, br s, NH), 3.61 (2H, m, 2- and 5-H), 4.14 (2H, dd, *J* 2.5 and 12.7 Hz, 1'- and 6'-H), 4.30 (2H, dd, *J* 0.9 and 12.7 Hz, 1- and 6-H), 4.45 (2H, d, *J* 2.5, 3- and 4-H), 5.49 (2H, s, PhC*H*), 7.46—7.50 (10H, m, Ph); *m/z* (CI, NH_3) 340 (100%, MH^+) (Found: C, 70.3; H, 6.2; N, 4.3. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

(2S,5S)-*Bishydroxymethyl*-(3R,4R)-*bishydroxypyrrolidine* (1). A solution of the pyrrolidine (5) (142 mg, 0.42 mmol) in aqueous trifluoroacetic acid (60% v/v; 20 ml) was

kept at room temperature for 48 h. Evaporation of the solvent gave an oil which was dissolved in water (10 ml) and the resultant solution washed with ether (3 X) to remove the benzaldehyde. The aqueous layer was concentrated to give a syrup which was redissolved in water (5 ml) and the solution deanionised with Amberlite CG-400 resin (OH^- form). Solvent removal provided a syrup which crystallised from ethanol to yield the *hydroxylated alkaloid* (1) (61 mg, 88%), m.p. 161—162 °C; $[\alpha]_D^{20}$ +14.3° (*c* 0.93, H_2O); δ(D_2O) 4.16 (2H, ddd, *J* 6.8, 6.6, and 4.0 Hz, 2- and 5-H), 4.38 (2H, dd, *J* 6.6 and 10.9 Hz, 1'- and 6'-H), 4.49 (2H, dd, *J* 6.8 and 10.9 Hz, 1- and 6-H), 4.91 (2H, d, *J* 4.0 Hz, 3- and 4-H); *m/z* (CI, NH_3) 164 (100%, MH^+) (Found: C, 44.6; H, 8.3; N, 8.7. $C_6H_{13}NO_4$ requires C, 44.2; H, 8.0; N, 8.6%).

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