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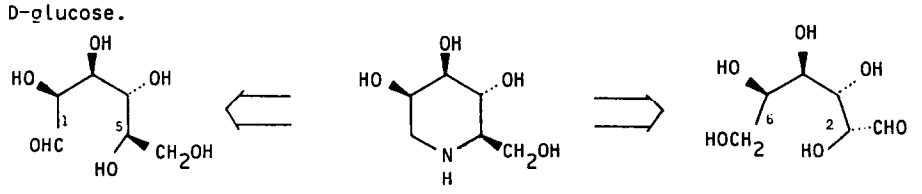
SYNTHESES OF 1,5-DIDEOXY-1,5-IMINO-D-MANNITOL FROM D-MANNOSE AND FROM D-GLUCOSE

G.W.J. Fleet, M.J. Gough and T.K.M. Shing

Dyson Perrins Laboratory, Oxford University,
South Parks Road, Oxford, U.K.

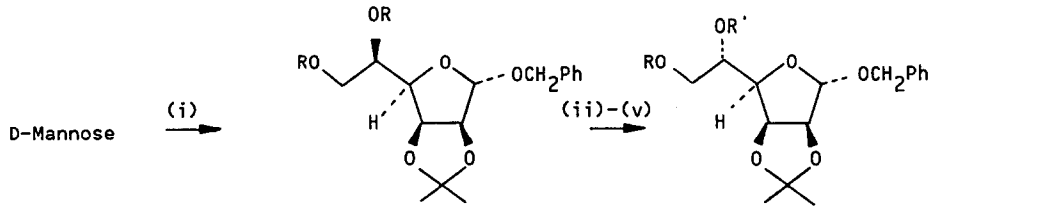
Abstract: Unambiguous enantiospecific syntheses of 1,5-dideoxy-1,5-imino-D-mannitol (LU1, 1-deoxy-mannojirimycin) are reported (i) from D-mannose via hydrogenation of a 5-azido-5-deoxy mannose, and (ii) from D-glucose, in which the key step involves nucleophilic substitution of a trifluoromethanesulphonyl group from C-2 of D-glucose.

Simple polyhydroxylated alkaloids provide a class of compounds which show great promise for the control of enzyme mediated transformations involving carbohydrate substrates, including glycosidase and transglycosylase activity. Nojirimycin, deoxynojirimycin and castanospermine inhibit various glucosidases, including a processing glucosidase of glycoprotein synthesis. Swainsonine and 1,5-dideoxy-1, 5-imino-D-mannitol (1), isolated from Lonchocarpus sericeus and characterised as the hydrochloride,[1] are mannosidase inhibitors; in particular, each inhibits a different mannosidase of glycoprotein processing.[2] Syntheses of swainsonine from methyl α-D-glucopyranoside in an overall yield of 1%,[3] and from benzyl α-D-mannopyranoside in an overall yield of 23%[4] have been reported recently. The first reported synthesis of deoxymannojirimycin (1) was from D-mannose in an overall yield of 14% using an enzymic oxidation; however, no characterisation of the compound was given.[5] The acetate salt of deoxymannojirimycin has been prepared from D-glucuronolactone in a multi step synthesis with an overall yield of less than 1%; a key step involved azidonitration of a glycal proceeding in only 6% yield.[6] The polyhydroxylated piperidine (1) may be derived by introduction of an amino function either between C-1 and C-5 of D-mannose, in a sequence involving a double inversion at C-5, or between C-6 and C-2 of D-glucose, with a single inversion of configuration of C-2 (Scheme 1). This paper describes enantiospecific syntheses of 1,5-dideoxy-1,5-imino-D-mannitol (1) as the free base from both D-mannose and D-glucose.



D-Mannose (1) D-Glucose

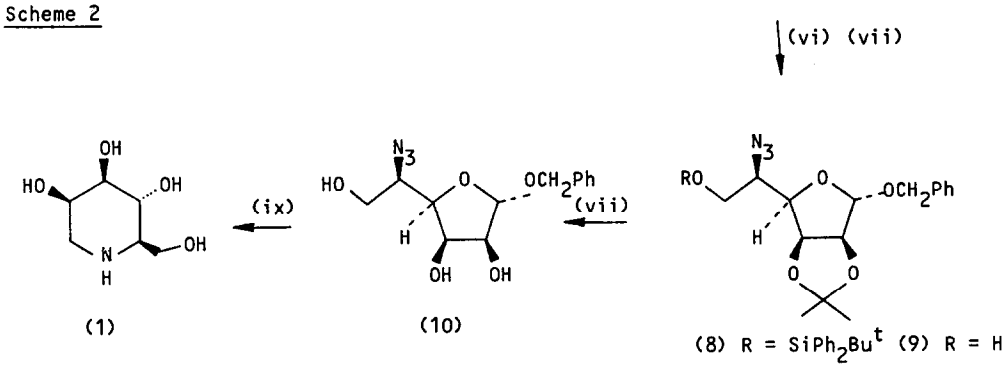
Scheme 1



(2) R = H
(3) R = SO_2Me

(4) R = R' = CO.Me (5) R = R' = H
(6) R = $SiPh_2Bu^t$, R' = H
(7) R = $SiPh_2Bu^t$, R' = SO_2CF_3

Scheme 2

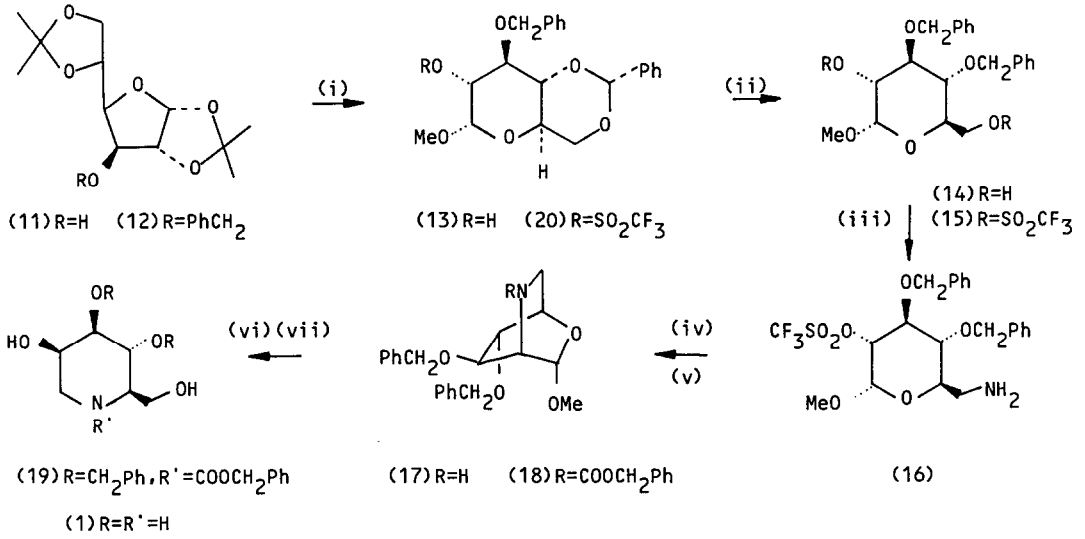


(1) (10) (8) R = $SiPh_2Bu^t$ (9) R = H

(i) Ref 7, then MsCl, pyridine, room temp (ii) NaOAc, Ac_2O, DMF, heat (iii) NaOMe, MeOH, room temp (iv) Ph_2SiBu^tCl, pyridine, room temp (v) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, -15° (vi) Bu_4NN_3, DMF, room temp (vii) Bu_4NF, THF, room temp (viii) CF_3COOH, dioxane, water (ix) palladium hydroxide, H_2, MeOH.

(i) From D-Mannose The strategy in this synthesis requires the synthesis of an intermediate 5-azidomannose (10) which on hydrogenation yields the required piperidine (1). In order to acheive the introduction of an azide function at C-5 of D-mannose with overall retention of configuration, it is necessary to protect C-1 to C-4 of mannose until a late stage in the synthesis; D-mannose may readily be converted to crystalline benzyl 2,3-O-isopropylidene-α-D-mannofuranoside (2) in 71% yield[7] (Scheme 2). The diol (2), in which only the C-5 and C-6 hydroxyl groups are free, with mesyl chloride in pyridine gave the dimesylate (3) which on subsequent treatment with sodium acetate yielded the diacetate (4). Removal of the ester groups by a catalytic amount of sodium methoxide in methanol formed benzyl 2,3-O-isopropylidene-β-L-gulofuranoside (5), m.p. 142-143°, $[\alpha]_D^{25}$ + 87.1° (c,1.1 in $CHCl_3$);[8,9] the inversion of the C-5 hydroxyl function was acheived in an overall yield of 62% from the manno-epimer (2). Protection of the primary hydroxyl group in (5)- by treatment with t-butyldiphenylsilyl chloride in pyridine to give (6)- was followed by esterification of the C-5 hydroxyl by triflic anhydride in the presence of pyridine; the resulting triflate (7) on treatment with tetrabutylammonium azide in DMF at room temperature underwent nucleophilic substitution with inversion to form the azidomannose (8) from which the silyl protecting group was removed by tetrabutylammonium fluoride to give benzyl 5-azido-5-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (9), m.p. 109-110° $[\alpha]_D^{20}$ + 68.4° (c, 0.6 in $CHCl_3$) [54% yield from (5); 33% overall yield from (2)]. Benzyl 5-azido-5-deoxy-α-D-mannofuranoside (10),

formed by hydrolysis of the acetonide in (9) by aqueous trifluoroacetic acid in dioxane, underwent hydrogenation in the presence of palladium hydroxide in methanol to form deoxymannojirimycin (1) $[\alpha]_D^{20}$ -34° (c, 0.3 in MeOH) in quantitative yield. The conversion of (10) to (1) involves reduction of the azide to the corresponding amine which on subsequent hydrogenolysis of the anomeric benzyl protecting group forms a lactol in equilibrium with an aminoaldehyde which then undergoes an intramolecular reductive amination to form the required piperidine; this sequence is similar to the construction of a pyrrolidine ring in the synthesis of swainsonine by hydrogenation of a benzyl 4-azido-4-deoxymannopyranoside derivative.[4]

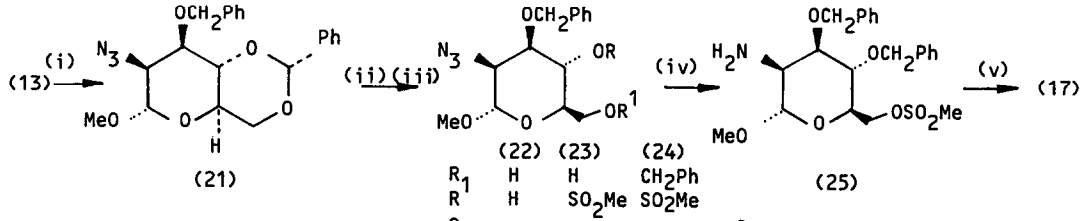


(i) 5% HCl in MeOH, then PhCHO, $ZnCl_2$ (ii) $LiAlH_4$ $AlCl_3$ in Et_2O (iii) $(CF_3SO_2)_2O$, pyridine in CH_2Cl_2, then liquid NH_3 (iv) Dimethylformamide, 35°, 7 d (v) $PhCH_2OCOCl$, EtOAc, H_2O containing $NaHCO_3$ (vi) 60% CF_3COOH in H_2O, room temp., then $NaBH_4$ in EtOH (vii) Pd black in AcOH.

Scheme 3

(ii) From D-Glucose The key intermediate in the synthesis of deoxymannojirimycin (1) from D-glucose is the bicyclic amine (17); the piperidine ring may be constructed either by intramolecular nucleophilic displacement of a triflate at position 2 in a 6-aminoglucose derivative (16) (Scheme 3) or, alternatively, by intramolecular nucleophilic displacement of a 6-mesylate in a 2-aminomannose derivative (25) (Scheme 4).

3-O-Benzyl 1,2:5,6-di-O-isopropylideneglucofuranose (12), prepared by quantitative benzylation of diacetone glucose (11),[10] was treated with 5% HCl in methanol, followed by benzaldehyde in the presence of zinc chloride, to give methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (13) in 85% yield (Scheme 3). Hydrogenolysis of the benzylidene acetal (13) with lithium aluminium hydride - aluminium chloride gave the 3,4-di-O-benzyl ether (14), m.p. 100-101° $[\alpha]_D^{20}$ +81° (c, 0.1 in $CHCl_3$) [lit.[11] m.p. 95-96° $[\alpha]_D^{20}$ +69° (c, 0.8 in $CHCl_3$)] (73% yield). Treatment of the diol (14) with triflic anhydride gave the ditriflate (15) which reacted with liquid ammonia to form the aminotriflate (16), m.p. 71-73° resulting from preferential nucleophilic displacement of the primary triflate [83% yield from (14)]. Ring closure by intramolecular nucleophilic displacement of triflate by the 6-amino group in (16) occurred on standing in DMF at 35° over several days to give the bicyclic amine (17)



(i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, -15^o; then NaN_3 in DMF, 60^o (ii) MeCOOH, H_2O; then $MeSO_2Cl$, pyridine (iii) $PhCH_2Br$, Ag_2O, DMF, room temp (iv) H_2, Pd/C, EtOAc (v) dimethylformamide, 50^o, 4 d.

Scheme 4

(55% yield) which was converted to the corresponding benzyl carbamate (18), $[\alpha]_D^{20}$ $+3.2^o$(c,0.1 in $CHCl_3$) on treatment with benzyl chloroformate (83% yield). Hydrolysis of the cyclic acetal function in (18) by aqueous trifluoroacetic acid, followed by the reduction of the resulting aldehyde by sodium borohydride, gave the protected piperidine (19) (87% yield). Hydrogenolysis of the protecting groups in the presence of palladium black gave 1,5-didexoy-1,5-imino-D-mannitol (1) (quantitative yield), identical in all respects to the sample prepared from D-mannose. The overall yield of (1) from diacetone glucose (11) is 23%.

Alternatively, esterification of the only free hydroxyl group in (13) with triflic anhydride gave the corresponding triflate (20), m.p. 93-94°, which on treatment with sodium azide in DMF gave the protected 2-azidomannose (21), $[\alpha]_D^{20}$ $+45.9^o$ (c,0.15 in $CHCl_3$) in 80% yield (Scheme 4). The benzylidene group in (21) was removed by partial hydrolysis with aqueous acetic acid and the resulting diol (22) reacted with mesyl chloride in pyridine to give the azidomesylate (23) (89% yield). The only remaining free hydroxyl group was protected as the benzyl ether (24) (77% yield), and partial hydrogenation of (24) in the presence of palladium on charcoal in ethyl acetate resulted only in reduction of the azide to the corresponding 2-aminomannose (25) in quantitative yield. Intramolecular nucleophilic displacement of the mesylate in (25) by the amino group occurs spontaneously in DMF at 50^o giving the cyclised piperidine (17) (79% yield) in an overall yield of 36% from diacetone glucose (11). Thus the overall yield of deoxymannojirimycin (1) from diacetone glucose by this route is 26%.

The characteristic relatively high field signals at 2.3 (1H) and 2.7 (2H) in the ^1H NMR in D_2O for the three protons adjacent to nitrogen in the free base (1) are shifted downfield on addition of trifluoroacetic acid; the NMR of the trifluoroacetate salt of (1) is consistent with the published data for the NMR of the hydrochloride[1] and acetate[6] of 1,5-dideoxy-1,5-imino-D-mannitol (1). In summary, this paper reports unambiguous and efficient syntheses of deoxymannojirimycin from both D-mannose and D-glucose.[12]

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