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ENANTIOSPECIFIC SYNTHESES OF DEOXYMANNOJIRIMYCIN, FAGOMINE AND 2R,5R-DIHYDROXYMETHYL-3R,4R-DIHYDROXYPYRROLIDINE FROM D-GLUCOSE

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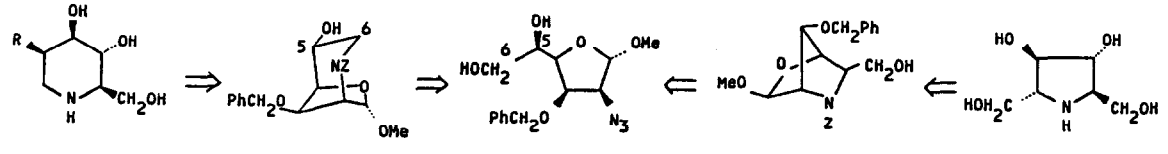
Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (4), readily available from D-glucose, is a common intermediate in the enantiospecific syntheses of deoxymannojirimycin [1,5-dideoxy-1,5-imino-D-mannitol](1), fagomine [1,2,5-trideoxy-1,5-imino-D-arabino hexitol] (2) and 2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrolidine (3); these syntheses establish the absolute configurations of (2) and (3).

Deoxymannojirimycin (1), isolated from Lonchocarpus sericeus,[1] is a mannosidase inhibitor[2] and has recently been synthesised from both mannose and glucose.[2,3] Fagomine (2), detected in seed of Japanese buckwheat (Fagopyrum esculentum Moench),[4] is the first polyhydroxylated piperidine alkaloid to occur conjugated to a glycoside.[5] 2R,5R-Dihydroxymethyl-3R,4R-dihydroxypyrrolidine (3), initially isolated from the leaves of the tropical legume, Derris elliptica,[6] and later detected in seed of closely related Lonchocarpus sericeus,[7] is the only example of a polyhydroxylated pyrrolidine alkaloid; (3), an aza analogue of fructofuranose, is a potent inhibitor of viral glycoprotein processing glucosidase I,[8] yeast α-glucosidase, almond emulsin β-glucosidase, trehalase, invertase and xylosidase.[7] The relative, but not the absolute, configurations of (2)[4] and (3)[6] were established by NMR studies. This paper describes unambiguous enantiospecific syntheses of (1), (2) and (3), thereby establishing the absolute configuration of (2) and (3). In a recent synthesis of deoxymannojirimycin from glucose,[3] the piperidine ring was constructed by intramolecular nucleophilic attack by nitrogen between C-2 and C-6 of an aminomannopyranoside; this is not a suitable strategy for the syntheses of (2) and (3) since the original C-5 of glucose is protected in the pyranose ring and is not accessible. This paper describes the conversion of D-glucose to the azidomannofuranoside (4) which may be cyclised by intramolecular nucleophilic attack on C-6 to the bicyclic amine (5) in which the original C-5 hydroxyl of glucose is unprotected and may be modified conveniently leading to a synthesis of fagomine; (4) may also be elaborated by intramolecular attack by nitrogen on C-5 giving the alternative bicyclic amine (6), suitable for conversion to the polyhydroxypyrrolidine (3) (Scheme 1).

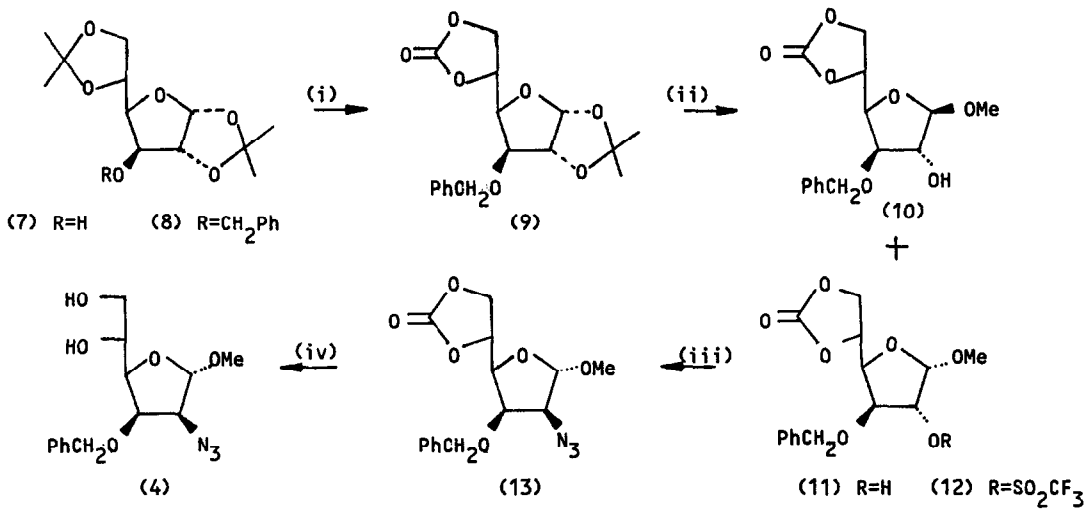


(1) R=OH
(2) R=H

(5) (4) (6) (3)

SCHEME 1

Z = $PhCH_2O.CO-$



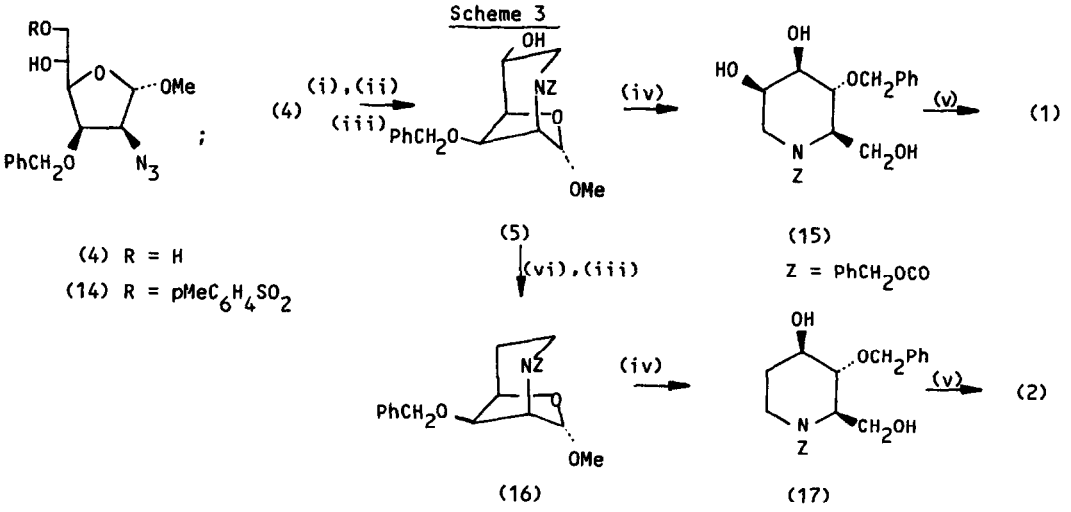
(i) 0.5% HCl in MeOH, room temp, 12 h; then $(MeO)_2CO$, NaOMe, reflux (ii) Dowex 50W-X8 resin (H^+ form), MeOH, reflux (iii) triflic anhydride (1.1 equiv), pyridine (2 equiv) in CH_2Cl_2, -20°, 20 min; then NaN_3 (3 equiv) dimethyl formamide, 50°, 2 d (iv) MeOH with a trace of NaOMe, room temp.

SCHEME 2

The 5,6-isopropylidene protecting group in 3-O-benzyl 1,2:5,6-di-O-isopropylideneglucofuranose (8), prepared by quantitative benzylation[9] of diacetone glucose (7), was selectively removed by HCl in methanol to give an intermediate diol, which on treatment with sodium methoxide (1 equiv) in dimethylcarbonate formed 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 5,6-carbonate (9), m.p. 119-120° (lit.[10] 119-120.5°) in an overall yield of 79% from diacetone glucose (7). The 5,6-carbonate (9) is readily prepared on 100 g scale without the need for any chromatographic purification and allows the construction of a furanose ring with only the C-2 hydroxyl group unprotected. Treatment of (9) with methanol in the presence of an acid ion exchange resin gives a mixture of β- and α- furanosides (10) and (11) in the ratio of 2.5:1 in 92% yield;[11] the anomers are separable by flash chromatography. Esterification of the α-anomer (11), $[\alpha]_D^{20}$ +88.6° (c, 1.3 in MeOH){(Lit.[10] $[\alpha]_D^{20}$ +93.3° (c,2.7 in MeOH)}, with trifluoromethanesulphonic anhydride, followed by displacement of the resulting triflate (12) with azide led to the formation of the azidomannofuranoside (13), $[\alpha]_D^{20}$ + 56.2° (c, 0.49 in $CHCl_3$).[12] The carbonate protecting group was removed by treatment of (13) with a trace of methoxide in methanol to give the easily crystallized azidodiol (4), m.p. 88-90°, $[\alpha]_D^{20}$ + 69.6° (c, 0.8 in MeOH) as the required key intermediate for the synthesis of the hydroxylated alkaloids (75% yield from (11)).

The formation of the piperidine ring required for the synthesis of deoxymannojirimycin and fagomine (Scheme 3) is achieved by intramolecular nucleophilic displacement of a leaving group at C-6 by an amino group at C-2. Thus the primary hydroxyl group in the azidodiol (4) was selectively tosylated and the sulphonate ester (14) was hydrogenated in the presence of palladium black. The resulting amine was treated with sodium acetate in ethanol, and subsequently with benzyl chloroformate, to give the bicyclic benzyl carbamate (5), an oil, $[\alpha]_D^{20}$ +39.5° (c, 0.41 in $CHCl_3$) [72% yield from (4)]. Hydrolysis of the acetal function in (5) by aqueous trifluoroacetic acid, followed by reduction with sodium borohydride gave (15)

Scheme 3

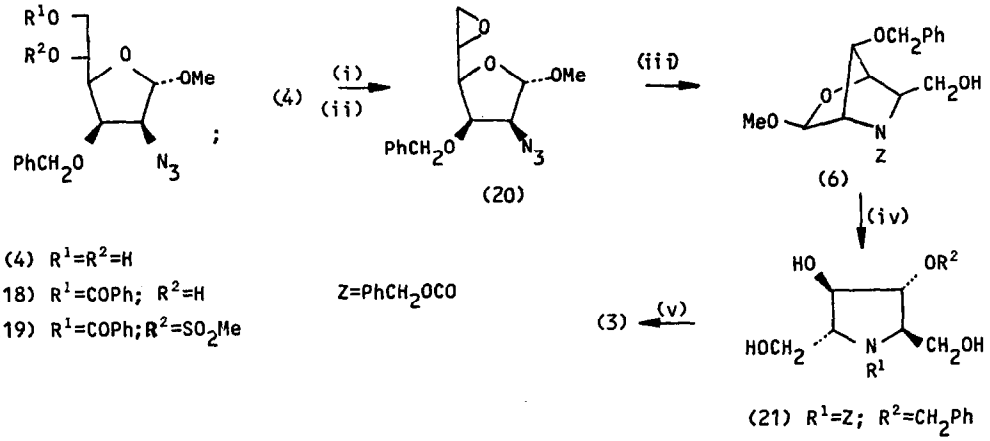


(i) p-toluene sulphonyl chloride (1.1 equiv), pyridine, room temp, 6 h (ii) palladium black, H_2 EtOH, 30 min; then NaOAc, EtOH, 50° (iii) $PhCH_2OCOCl$, ether, H_2O containing $NaHCO_3$ (iv) CF_3COOH - H_2O (1:1), room temp, 1 h; then $NaBH_4$ in EtOH - H_2O (v) palladium hydroxide, H_2, EtOH (vi) triflic anhydride, pyridine, -20°; then $LiBHEt_3$ in tetrahydrofuran.

(81% yield) [57% from (4)]; removal of the benzyl and benzyloxycarbonyl protecting groups by hydrogenolysis with palladium hydroxide catalyst gave deoxymannojirimycin (1), m.p. 185-187° $[\alpha]_D^{20}$ -26.7° (c, 0.12 in MeOH)[lit.[3] m.p. 186°, $[\alpha]_D^{20}$ -34° (c 0.3 in MeOH)], identical in all respects with an authentic sample.

The secondary hydroxyl group in (5) was removed by esterification with triflic anhydride followed by reduction of the corresponding triflate with lithium triethylborohydride in tetrahydrofuran; displacement of triflate in this reaction was accompanied by some removal of the carbamate protecting group, so the crude reaction mixture was treated with benzyl chloroformate and the deoxygenated bicyclic amine (16) was purified by flash chromatography as an oil, $[\alpha]_D^{20}$ +39.5° (c, 0.41 in $CHCl_3$). Acid hydrolysis, followed by sodium borohydride reduction, gave the protected fagomine (17) $[\alpha]_D^{20}$ -46.1° (c, 0.17 in $CHCl_3$) in 28% overall yield from (5) [20% from (4)]. Removal of the protecting groups by catalytic hydrogenation gave free fagomine, $[\alpha]_D^{20}$ +21.6° (c, 0.36 in H_2O) [lit.[5] $[\alpha]_D^{20}$ +24.7° (c, 0.4 in H_2O)] with the details of the ^1H NMR identical to those reported[4] and identical to a sample of authentic fagomine (2).[5,13]

Synthesis of the pyrrolidine (3) requires intramolecular nucleophilic attack with overall retention of configuration at C-5 by a nitrogen function derived from the azido group at C-2 in (4); this was achieved by two sequential inversions of configuration at C-5 (Scheme 4). Reaction of (4) with benzoyl chloride in pyridine at 0° gave selectively the benzoate ester (18), m.p. 73-74°, $[\alpha]_D^{20}$ +20.7° (c, 0.46 in $CHCl_3$) which with methane sulphonyl chloride formed (19). Treatment of (19) with sodium methoxide in dimethylformamide lead to the formation of the epoxide (20), $[\alpha]_D^{20}$ +19.5° (c, 0.58 in $CHCl_3$) in an overall yield of 77% from (4). Hydrogenation of the azidoepoxide (20), followed by cyclisation and protection of the amino function with benzyl chloroformate, gave the bicyclic amine (6), $[\alpha]_D^{20}$ +10.6°



(4) $R^1=R^2=H$
(18) R^1=COPh; $R^2=H$
(19) R^1=COPh; $R^2=SO_2Me$

Z=$PhCH_2OCO$

(i) PhCOCl (1.1 equiv), pyridine, 0°; then $MeSO_2Cl$, pyridine, room temp., 4 h (ii) NaOMe (2 equiv), dimethylformamide 50°, 5 h (iii) palladium black, H_2, EtOH; remove catalyst, then 50° overnight; $PhCH_2OCOCl$, ether, H_2O containing $NaHCO_3$ (iv) CF_3COOH - H_2O (1:1), room temp. 1 h; then $NaBH_4$ in EtOH - H_2O (v) palladium hydroxide, H_2, EtOH.

Scheme 4

(c, 0.52 in $CHCl_3$), in 43% yield [33% from (4)]; the major product from the cyclisation is derived from a 5-exo-tet process[14] - no product derived from a competing 7-endo-tet reaction was isolated. Acid catalysed hydrolysis of the bicyclic acetal (6), followed by sodium borohydride reduction, gave the protected hydroxypyrrolidine (21). Hydrogenolysis of the protecting groups using a palladium hydroxide catalyst gave 2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrolidine (3), $[\alpha]_D^{20}$ +53.8° (c, 0.41 in H_2O) [lit.[6] $[\alpha]_D^{20}$ + 56.4° (c, 7 in H_2O)] with identical spectral properties to those previously reported[6] and to an authentic sample.[13]

In summary this paper demonstrates the use of the azidodiol (4) as a divergent intermediate for the enantiospecific syntheses of the polyoxygenated alkaloids (1), (2) and (3) and establishes the absolute configurations of fagomine (2) and 2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrroldine (3).[15]

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11. We are currently studying the chemistry of the β furanoside (10); the present paper discusses the reactions of the pure α anomer (11).
12. Satisfactory spectral and/or analytical data were obtained for all new compounds.
13. We are grateful to Drs. L.E. Fellows and S.V. Evans of the Royal Botanic Gardens at Kew for providing authentic samples of the hydroxylated alkaloids.
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