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PRACTICAL SYNTHESIS OF DEOXYMANNOJIRIMYCIN AND MANNONOLACTAM FROM L-GULONOLACTONE. SYNTHESIS OF L-DEOXYMANNOJIRIMYCIN AND L-MANNONOLACTAM FROM D-GULONOLACTONE.

George W. J. Fleet, Nigel G. Ramsden and David R. Witty

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK

An eight step synthesis of deoxymannojirimycin from L-gulonolactone in 25% overall yield is reported; the key step is the formation of a δ-lactam by the reduction of a 5-azidolactone. The preparations of mannonolactam from L-gulonolactone and of L-deoxymannojirimycin and L-mannonolactam from D-gulonolactone are described.

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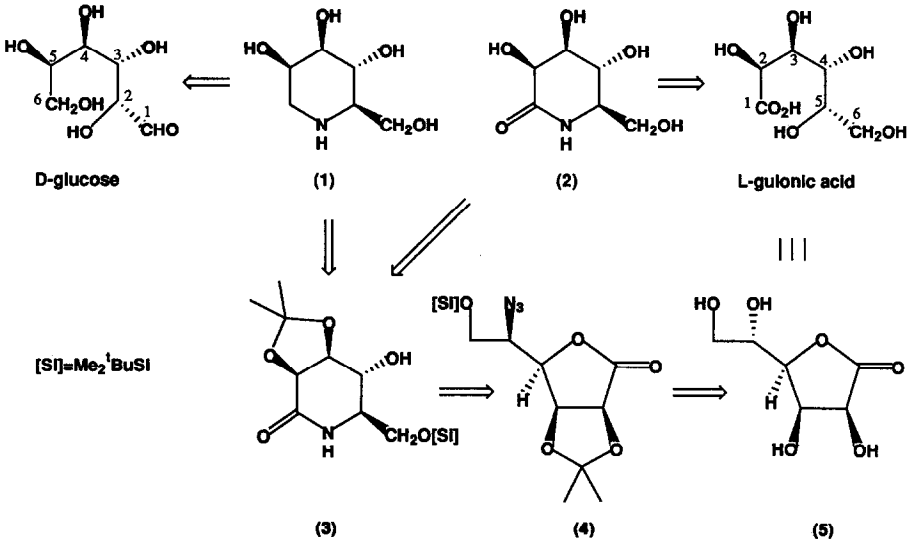
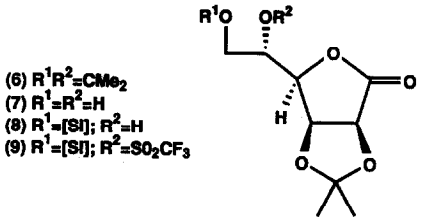
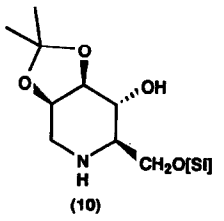
The ready availability of both enantiomers of gulonolactone,[1] combined with the ease of protection of different combinations of hydroxyl groups,[2] make them attractive starting materials for the enantiospecific synthesis of many highly functionalised compounds. Deoxymannojirimycin (1) has been synthesised by introduction of nitrogen with overall retention of configuration at C-5 of mannose[3] and the accompanying paper describes a practical synthesis from D-glucose by connection of C-2 and C-6 by nitrogen.[4] This paper describes a convenient synthesis of deoxymannojirimycin and of D-mannonolactam (2) in which the piperidine ring is derived by introducing azide with inversion of configuration at C-5 of L-gulonolactone (5); reduction of the resulting azidolactone (4) leads to the formation of the δ-lactam (3). The formation of δ-lactams from 5-azido-5-deoxy-1,4-lactones is a well-established procedure.[5] D-Mannonolactam (2) is a powerful inhibitor of rat epididymal α-mannosidase and of apricot β-glucosidase,[6] and other δ-lactams have been shown to be glycosidase inhibitors.[7] Recently, the lactam (3) and its enantiomer (16) have been used as intermediates in the synthesis of stereoisomers of castanospermine,[8] including the natural product 6-epicastanospermine, isolated from Castanospermum australe.[9]



Both L-gulonolactone (5)[10] and D-gulonolactone[11] have been used in short sequences for the preparation of polyhydroxylated pyrrolidines, and this paper also describes the synthesis of L-deoxymannojirimycin (18) and L-mannonolactam (17) from D-gulonolactone; a preliminary account of this work has been published.[12]





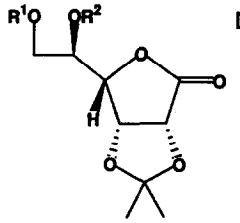
(10)

In order to introduce nitrogen with inversion at C-5 of L-gulonolactone, the hydroxyl groups at C-2, C-3 and C-6 were protected. L-Gulonolactone (5) with acetone/dimethoxypropane in the presence of a catalytic amount of p-toluenesulphonic acid gave 2,3;5,6-di-O-isopropylidene-L-gulonolactone (6)[13] [79% yield]; the side chain isopropylidene protecting group can be selectively hydrolysed by aqueous acetic acid to give 2,3-O-isopropylidene-L-gulonolactone (7) [79% yield]. The primary hydroxyl group in (7) was then protected as the corresponding tert-butyldimethylsilyl ether (8) in 71% yield. In principle, it was possible that initial protection of the C-6 hydroxyl in L-gulonolactone, followed by treatment with acetonating agents, would provide a shorter route to (8); however, all attempts to produce (8) by isopropylidenation of 6-O-tert-butyldimethylsilylgulonolactone gave the isomeric 6-O-tert-butyldimethylsilyl-3,5-O-isopropylidenegulonolactone in good yield.

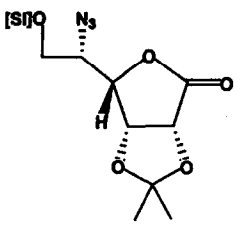
Conversion of the remaining alcohol in (8) to the trifluoromethanesulphonate ester (9), followed by treatment with sodium azide in dimethylformamide gave the inverted azide (4) in 76% yield. Use of tert-butyldiphenylsilyl protection, as an alternative to tert-butyldimethylsilylation, in this sequence gave lower overall yields; attempted displacement of the corresponding triflate by sodium azide gave negligible quantities of substitution product.

Hydrogenation of the azide (4) in methanol in the presence of palladium on carbon gave an amine which spontaneously rearranged to the lactam (3) [91% yield]; the interconversion of the intermediate amine to the lactam is solvent dependent, taking place very much more slowly in ethyl acetate. The lactam (3) was reduced to the borane complex of the corresponding amine (10) by treatment with borane:dimethyl sulphide complex; reaction of (10) with aqueous trifluoroacetic acid causes removal of all the protecting groups to give, after purification by ion exchange chromatography, deoxymannojirimycin (1) in 80% yield from (3). This sequence allows the easy preparation of several gram of deoxymannojirimycin in 25% overall yield from L-gulonolactone. Hydrolysis of lactam (3) gives mannonolactam (2) in 89% yield.

As part of a systematic study of the glycosidase inhibitory properties of polyhydroxylated piperidines and pyrrolidines, the enantiomers L-deoxymannojirimycin (18) and L-mannonolactam (17) were prepared by a similar route. D-Gulonolactone was converted[14] into 2,3:5,6-di-O-isopropylidene-D-gulonolactone (11) [82% yield] which was selectively hydrolysed to the diol (12)[15] [79% yield] and protected as the silyl ether (13) [71% yield]. Reaction of (13) with triflic anhydride afford the triflate (14) which on reaction with sodium azide gave the azidolactone (15) [72% yield]. Hydrogenation of the azide (15) in methanol in the



(11) R^1R^2=CMe_2
(12) R^1=R^2=H
(13) R^1=[Si]; R^2=H
(14) R^1=H; R^2=SO_2CF_3



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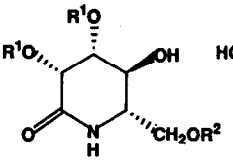
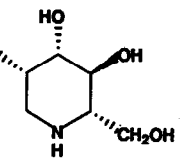


(16) R^1=Me_2C; R^2=[Si]
(17) R^1=R^2=H



(18)

presence of a palladium catalyst led to the δ-lactam (16) [76% yield] which was hydrolysed to L-mannonolactam (17) in 91% yield. Reduction of (16) with borane:dimethyl sulphide, followed by acid treatment, gave L-deoxymannojirimycin (18) [72% yield].

In summary, this paper reports a practical synthesis of deoxymannojirimycin from L-gulonolactone in an overall yield of 25%; the synthesis of mannonolactam and of L-deoxymannojirimycin and of L-mannonolactam are also described. The accompanying paper[4] describes an alternative synthesis of deoxymannojirimycin from D-glucose.[16]

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. All NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for NMR spectra in D_2O, 1,4-dioxane (δ 67.6) was used as the internal standard. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 0.2% w/v concentrated sulphuric acid and 5% ammonium molybdate in 2M sulphuric acid. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. Tetrahydrofuran was distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen. D- and L-Gulonolactone were obtained from Sigma Chemical Company. Purification of compounds by ion exchange used Aldrich Chemical Company 50x 8-100 resin (H^+ form), eluting with aqueous ammonia (0.5 M).

2,3:5,6-Di-O-isopropylidene-L-gulonolactone (6). L-Gulonolactone (5) (20.00 g, 112.3 mmol) was stirred with acetone (160 ml), 2,2-dimethoxypropane (40 ml) and a catalytic amount of p-toluenesulphonic acid under dry nitrogen for 36 h when TLC (ethyl acetate) revealed no starting material (R_f 0.0) and one product (R_f 0.9). The reaction mixture was stirred with an excess of sodium bicarbonate and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (200 ml) and washed with water (3 x 200 ml). The organic extracts were dried (magnesium sulphate) and the solvent removed under reduced pressure to give a solid which was recrystallised from ethyl acetate to yield 2,3:5,6-di-O-isopropylidene-L-gulonolactone (6), (22.89 g, 79%), m.p. 151°-153°C. $[\alpha]_D^{20}$ +68.4° (c, 1 in acetone) [lit.[13] m.p. 153°-154°C. $[\alpha]_D^{24}$ +91.5° (c, 1)]. δ_C ($CDCl_3$); 173.3 (s, C-1), 114.7 (s), 110.5 (s), 80.9, 76.0, 75.7 and 75.2 (4xd, C-2, C-3, C-4 and C-5), 65.1 (d, C-6), 26.5 (q), 25.7 (q), 25.0 (q).

2,3-O-Isopropylidene-L-gulonolactone (7). 2,3:5,6-Di-O-isopropylidene-L-gulonolactone (6) (22.89 g, 88.7 mmol) was dissolved in acetic acid/water (7:1, 200 ml) and stirred at 30°C for 16 h when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.5) and one major product (R_f 0.1). The solvent was removed under reduced pressure to give a yellow oil. Trituration with benzene (50 ml) gave a solid which was shaken with ethyl acetate/acetone (1:1, 250 ml). The resulting suspension was filtered and solvents removed under reduced pressure to yield an amorphous yellow solid, which was recrystallised from ethyl acetate to yield 2,3-O-isopropylidene-L-gulonolactone (7), (14.31 g, 79%) as a white crystalline solid, m.p. 139°-141°C, $[\alpha]_D^{20}$ +76.2° (c, 1 in acetone).

6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-L-gulonolactone (8). 2,3-O-Isopropylidene-L-gulonolactone (7) (14.3 g, 65.6 mmol) was stirred in dry dimethylformamide (100 ml) and the solution cooled to -40°C under dry nitrogen. Imidazole (6.86g, 98.4mmol) and tert-butyldimethylsilyl chloride (10.9 g, 72.2 mmol) were added. The reaction was stirred at -40°C for 2 h when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.1) and one major product (R_f 0.8). The solvent was removed under reduced pressure and the residue was dissolved in brine (200 ml) and extracted with dichloromethane (3 x 200 ml). The organic extracts were dried (magnesium sulphate) and the solvent removed under reduced pressure to give a colourless oil. Purification by flash column chromatography (ethyl acetate/hexane 1:3) gave 6-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-L-gulonolactone (8), (15.44 g, 71%) as a colourless oil, $[\alpha]_D^{20}$ +51.6° (c, 0.64 in $CHCl_3$), m/z (CI NH_3); 350 ($M+NH_4^+$, 100%). δ_H ($CDCl_3$); 4.85 (2H, m), 4.58 (1H, dd), 4.07 (1H, m), 3.83 (2H, dd), 2.71 (1H, d, OH), 1.50 and 1.41 (2x3H, 2xs), 0.92 (9H, s), 0.11, (6H, s). δ_C ($CDCl_3$); 173.7 (s, C-1), 114.6 (s), 79.1, 76.4, 76.3 and 70.9 (4xd, C-2, C-3, C-4 and C-5), 63.1 (t, C-6), 26.65 (q), 25.7 (q), 25.6 (q), 18.1 (s), -5.6 (q).

5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-mannonolactone (4). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-L-gulonolactone (8) (15.44 g, 46.4 mmol) was dissolved in dry dichloromethane (100 ml) and pyridine (11.19 ml, 138.8 mmol) was added. The reaction was cooled to -30°C under dry nitrogen. Trifluoromethanesulphonic anhydride (16.1 ml, 95.8 mmol) was added and the reaction was stirred for 1 h when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.8) and one product (R_f 0.9). The reaction mixture was then diluted with dichloromethane (100 ml) and washed with aqueous hydrochloric acid (2M, 100 ml), water (100 ml) and saturated sodium bicarbonate (100 ml). The organic layer was dried (magnesium sulphate) and the solvent removed under reduced pressure to give the crude triflate (9) which was dissolved in dry dimethylformamide (75 ml) and stirred under dry nitrogen with sodium azide (9.0 g, 139.3 mmol). After 3 h TLC (ethyl acetate/hexane 1:3) showed no starting material (R_f 0.4) and one product (R_f 0.5). The solvent was removed under reduced pressure and the residue dissolved in brine (100 ml). This was extracted with dichloromethane (3 x 100 ml). The organic extracts were combined, dried (magnesium sulphate) and the solvents removed under reduced pressure to give a crude yellow oil. Elution through a silica plug (ethyl acetate/hexane 1:3) gave a colourless oil which crystallized on standing. Recrystallisation from hexane yielded 5-azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-mannonolactone (4), (12.6 g, 76%), m.p. 86°-87°C. $[\alpha]_D^{20}$ -9.6° (c, 3 in $CHCl_3$). ν_{max} ($CHCl_3$); 2100 (N_3), 1760 (C=O) cm^{-1}. m/z (DCI NH_3); 347 ($M+NH_4^+$), 319 ($M+NH_4-N_2^+$). δ_H ($CDCl_3$); 4.8 (2H, m, H-2 and H-3, $J_{2,3}$ 5.18 Hz), 4.40 (1H, dd, H-4, $J_{3,4}$ 3.25 Hz), 4.06 (1H, dd, H-6', $J_{6,6'}$ 10.81 Hz, $J_{6',5}$ 5.43 Hz),

3.87 (1H, dd, H-6, $J_{6,5}$ 2.32 Hz), 3.75 (1H, ddd, H-5, $J_{5,4}$ 10.02 Hz), 1.50 and 1.45 (2 x 3H, 2s), 0.93 (9H, s), 0.12 (6H, s). δ_C ($CDCl_3$); 173.6 (s, C-1), 114.4 (s), 76.4, 75.9 and 75.4 (3d, C-2, C-3 and C-4), 63.1 (t, C-6), 60.4 (d, C-5), 26.8 (q), 26.0 (q), 25.7 (q), 18.2 (s), -5.6 (q). (Found: C, 50.42; H, 7.72; N, 12.05%. $C_{15}H_{27}O_5N_3Si$ requires C, 50.42; H, 7.56; N, 11.76%).

6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-D-mannono-δ-lactam (3). 5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-mannonolactone (11.69 g, 32.8 mmol) was dissolved in methanol (50 ml) and stirred under hydrogen with a catalytic amount of 10% palladium on carbon for 14 h when TLC (ethyl acetate/hexane 1:3) revealed baseline material only and TLC (10% methanol in dichloromethane) showed one major product (R_f 0.5). The reaction mixture was filtered through a celite plug which was washed with methanol. Solvents were removed under reduced pressure to give a colourless oil. Purification by flash column chromatography (ethyl acetate) yielded 6-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-D-mannono-δ-lactam (3), (9.88 g, 91%), as a white crystalline solid, m.p. 104°-105°C, $[\alpha]_D^{20}$ +19.2° (c, 1.02 in $CHCl_3$). γ max ($CHCl_3$); 3300cm^{-1} (br, OH and NH), 1670cm^{-1} (C=O). m/z (ACE NH_3); 332 ($M+H^+$), 274 ($M+H-CH_3COCH_3^+$). δ_H ($CDCl_3$); 6.18 (br, NH), 4.63 (1H, d, H-2), 4.30 (1H, dd, H-3), 4.00 (1H, dd, H-6'), 3.59 (2H, m, H-6 and H-4), 3.37 (1H, m, H-5), 1.52 and 1.41 (2x3H, 2xs), 0.89, (9H, s), .09 (6H, s). δ_C ($CDCl_3$); 168.6 (s, C-1), 110.8 (s), 78.8, 72.8 and 70.8 (3xd, C-2, C-3 and C-4), 63.3 (t, C-6), 54.7 (d, C-5), 26.9 (q), 24.8 (q), 25.6 (q), 17.95 (s), -5.7 (q). (Found: C, 54.19; H, 8.56; N, 4.26%. $C_{15}H_{29}O_5N$ requires C, 54.38; H, 8.76; N, 4.23%).

Deoxymannojirimycin (1). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-D-mannono-δ-lactam (3) (9.88 g, 29.6 mmol) was dissolved in dry tetrahydrofuran (50 ml) and stirred under dry nitrogen. Borane/dimethyl sulphide complex (10 M, 8.89 ml) was added and the reaction was stirred for 2 h when TLC (ethyl acetate) revealed no starting material (R_f 0.5) and one product (R_f 0.9). The reaction was quenched by cautious addition of methanol until effervescence had ceased. Solvents were removed under reduced pressure and methanol (3 x 50 ml) was distilled from the residue. The residue was dissolved in trifluoroacetic acid/ water (2:1, 15 ml). The reaction was left to stand for 2 h when TLC (ethyl acetate) revealed baseline material only. Solvents were removed under reduced pressure and toluene (3 x 20 ml) was distilled from the reaction mixture. The residue was purified by ion exchange chromatography to yield deoxymannojirimycin which was converted to its hydrochloride salt by treatment with aqueous hydrochloric acid (0.5M). This was further purified by recrystallisation from methanol to give deoxymannojirimycin hydrochloride, (4.50 g, 80%), m.p. 185°-186°C, $[\alpha]_D^{20}$ -15.3° (c, 0.50 in water), m/z (CI NH_3); 164 ($M+H^+$, 100%), 128, 110. δ_H (D_2O); 4.10 (1H, ddd, H-2), 3.72 (1H, dd, H-4), 3.69 (1H, dd, H-6), 3.54 (1H, dd, H-3), 3.27 (1H, dd, H-1'), 3.10 (1H, dd, H-1), 3.01 (1H, ddd, H-5). δ_C (D_2O); 73.1 (d, C-2), 66.6 (d), 66.5 (d), 61.1 (d, C-5), 58.8 (t, C-6), 48.3 (t, C-1).

D-Mannono-δ-lactam (2). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-D-mannono-δ-lactam (3) (98 mg, 0.3 mmol) was dissolved in trifluoroacetic acid/water (1:1, 5 ml) and left to stand for 1 h when TLC (10% methanol in chloroform) revealed no starting material (R_f 0.5) and TLC (2:1 chloroform/methanol) revealed one product (R_f 0.5). The solvent was removed under reduced pressure and toluene (3 x 5 ml) was distilled from the residue. Trituration with ether gave a white crystalline solid which was recrystallised from methanol to give D-mannono-δ-lactam (2), (46 mg, 89%), m.p. 165°-169°C, $[\alpha]_D^{20}$ +0.9° (c, 1.0 in water) (lit.[6] m.p. 168°-170°C,

$[\alpha]_D^{20}$ +1.6° (c, 1.0 in water). m/z (DCI NH_3); 178 ($M+H^+$, 100%), 112. δ_H (D_2O); 4.16 (1H, d, H-2), 3.83 (1H, dd, H-3), 3.68 (1H, dd, H-4), 3.54 (2H, m, H-6 and H-6'), 3.19 (1H, m, H-5). δ_C (D_2O); 173.5 (s, C-1), 71.9 (d, C-3), 68.2 (d, C-2), 67.1 (d, C-4), 61.1 (t, C-6), 57.3 (d, C-5).

2,3:5,6-Di-O-isopropylidene-D-gulonolactone (11). D-Gulonolactone (15.47 g, 86.9 mmol) was stirred with acetone (160 ml), 2,2-dimethoxypropane (40 ml) and a catalytic amount of p-toluenesulphonic acid under dry nitrogen for 36 h when TLC (ethyl acetate) revealed no starting material (R_f 0.0) and one product (R_f 0.9). The reaction mixture was stirred with an excess of sodium bicarbonate and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (200 ml) and washed with water (3 x 200 ml). The organic extracts were dried (magnesium sulphate) and the solvent removed under reduced pressure to give a solid which was recrystallised from ethyl acetate to yield 2,3:5,6-di-O-isopropylidene-D-gulonolactone (18.38g, 82%), m.p. 151°-153°C, $[\alpha]_D^{20}$ -70.0° (c, 1.0 in acetone) [lit.[14,15] m.p. 152°-153°C, $[\alpha]_D^{20}$ -64.0° (c, 2.8 in acetone)]. δ_C ($CDCl_3$); 173.3 (s, C-1), 114.7 (s), 110.5 (s), 80.9, 76.0, 75.7 and 75.2 (4xd, C-2, C-3, C-4 and C-5), 65.1 (d, C-6), 26.5 (q), 25.7 (q), 25.0 (q).

2,3-O-Isopropylidene-D-gulonolactone (12). 2,3:5,6-Di-O-isopropylidene-D-gulonolactone (11) (18.25 g, 70.7 mmol) was dissolved in acetic acid/water (7:1, 200 ml) and stirred at 30°C for 16 h when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.5) and one major product (R_f 0.1). The solvent was removed under reduced pressure to give a yellow oil. Trituration with benzene (50 ml) gave a solid which was shaken with ethyl acetate/acetone (1:1, 250 ml). The resulting suspension was filtered and solvents removed under reduced pressure to yield an amorphous yellow solid which was recrystallised from ethyl acetate to yield 2,3-O-isopropylidene-D-gulonolactone, (12.18 g, 79%), m.p. 139°-141°C, $[\alpha]_D^{20}$ -79.4° (c, 1 in acetone) [lit.[15] m.p. 142°-143°C, $[\alpha]_D^{20}$ -76.5° (c, 2.8 in acetone)].

6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-D-gulonolactone (13). 2,3-O-Isopropylidene-D-gulonolactone (12) (8.03 g, 36.8 mmol) was stirred in dry dimethylformamide (75 ml) and the solution cooled to -40°C under dry nitrogen. Imidazole (3.75 g, 55.2 mmol) and tert-butyldimethylsilyl chloride (6.10 g, 40.5 mmol) were added. The reaction was stirred at -40°C for 2 hr when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.1) and one major product (R_f0.8). The solvent was removed under reduced pressure, the residue was dissolved in brine (200 ml) and extracted with dichloromethane (3 x 200 ml). The organic extracts were dried (magnesium sulphate) and the solvent removed under reduced pressure to give a colourless oil. Purification by flash column chromatography (ethyl acetate/hexane 1:3) gave 6-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-D-gulonolactone, colourless oil, (8.67g, 71%), $[\alpha]_D^{20}$ -46.5° (c, 0.5 in $CHCl_3$), m/z (CI NH_3); 350 ($M+NH_4^+$, 100%). δ_H ($CDCl_3$); 4.85 (2H, m), 4.58 (1H, dd), 4.07 (1H, m), 3.83 (2H, dd), 2.71 (1H, d, OH), 1.50 and 1.41 (2 x 3H, 2s), 0.92 (9H, s), 0.11, (6H, s). δ_C ($CDCl_3$); 173.7 (s, C-1), 114.6 (s), 79.1, 76.4, 76.3 and 70.9 (4d, C-2, C-3, C-4 and C-5), 63.1 (t, C-6), 26.65 (q), 25.7 (q), 25.6 (q), 18.1 (s), -5.6 (q).

5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-L-mannonolactone (15). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-D-gulonolactone (13) (8.91 g, 26.8 mmol) was dissolved in dry dichloromethane (50 ml) and pyridine (6.46 ml, 80.1 mmol) was added. The reaction was cooled to -30°C under dry nitrogen.

Trifluoromethanesulphonic anhydride (9.28 ml, 55.3 mmol) was added and the reaction was stirred for 1 h when TLC (ethyl acetate/hexane 1:1) revealed no starting material (R_f 0.8) and one product (R_f 0.9). The reaction mixture was then diluted with dichloromethane (50 ml) and washed with aqueous hydrochloric acid (2M, 100 ml), water (100 ml) and saturated sodium bicarbonate (100 ml). The organic layer was dried (magnesium sulphate) and the solvent removed under reduced pressure to give crude 6-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-5-O-trifluoromethanesulphonyl-D-gulonolactone (14), which without purification, was dissolved in dry dimethylformamide (50 ml) and stirred under dry nitrogen with sodium azide (5.2 g, 80.4 mmol). After 3 h, TLC (ethyl acetate/hexane 1:3) showed no starting material (R_f 0.4) and one product (Rf 0.5). The solvent was removed under reduced pressure and the residue dissolved in brine (100 ml), extracted with dichloromethane (3 x 100 ml); the organic extracts were combined, dried (magnesium sulphate) and the solvents removed under reduced pressure to give a crude yellow oil. Elution through a silica plug (ethyl acetate/hexane 1:3) gave a colourless oil which crystallized on standing, to afford, after recrystallisation from hexane, 5-azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-L-mannonolactone (15), (6.89 g, 72%), m.p. 86°-87°C, $[\alpha]_D^{20}$ +8.6° (c, 1.1 in $CHCl_3$), ν_{max} ($CHCl_3$); 2100 (N_3), 1760 (C=O), cm^{-1}. m/z (DCI NH_3); 347 ($M+NH_4^+$), 319 ($M+NH_4-N_2^+$). δ_H ($CDCl_3$); 4.8 (2H, m, H-2 and H-3, $J_{2,3}$ 5.18 Hz), 4.40 (1H, dd, H-4, $J_{3,4}$ 3.25 Hz), 4.06 (1H, dd, H-6', $J_{6,6'}$ 10.81 Hz, $J_{6',5}$ 5.43 Hz), 3.87 (1H, dd, H-6, $J_{6,5}$ 2.32 Hz), 3.75 (1H, ddd, H-5, $J_{5,4}$ 10.02 Hz), 1.50 and 1.45 (2 x 3H, 2s), 0.93 (9H, s), 0.12 (6H, s). δ_C ($CDCl_3$); 173.6 (s, C-1), 114.4 (s), 76.4, 75.9 and 75.4 (3d, C-2, C-3 and C-4), 63.1 (t, C-6), 60.4 (d, C-5), 26.8 (q), 26.0 (q), 25.7 (q), 18.2 (s), -5.6 (q). (Found: C, 50.42; H, 7.72; N, 12.05%. $C_{15}H_{27}O_5N_3Si$ requires C, 50.42; H, 7.56; N, 11.76%).

6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-L-mannono-δ-lactam (16). 5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-L-mannonolactone (15) (5.91 g, 16.6 mmol) was dissolved in methanol (25 ml) and stirred under hydrogen with a catalytic amount of 10% palladium on carbon for 14 h when TLC (ethyl acetate/hexane 1:3) revealed baseline material only and TLC (10% methanol in dichloromethane) showed one major product (R_f 0.5). The reaction mixture was filtered through a celite plug which was washed with methanol (3 x 10 ml). Solvents were removed under reduced pressure to give a colourless oil, which after purification by flash column chromatography (ethyl acetate), yielded 6-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-L-mannono-δ-lactam, (4.14g, 76%), m.p. 104°-105°C, $[\alpha]_D^{20}$ -17.9° (c, 0.86 in $CHCl_3$), ν_{max} ($CHCl_3$); 3300 (br, OH and NH), 1670 (C=O) cm^{-1}. m/z (ACE NH_3); 332 ($M+H^+$), 274 ($M+H-CH_3COCH_3^+$). δ_H ($CDCl_3$); 6.18 (br, NH), 4.63 (1H, d, H-2), 4.30 (1H, dd, H-3), 4.00 (1H, dd, H-6'), 3.59 (2H, m, H-6 and H-4), 3.37 (1H, m, H-5), 1.52 and 1.41 (2 x 3H, 2s), 0.89, (9H, s), .09 (6H, s). δ_C ($CDCl_3$); 168.6 (s, C-1), 110.8 (s), 78.8, 72.8 and 70.8 (3d, C-2, C-3 and C-4), 63.3 (t, C-6), 54.7 (d, C-5), 26.9 (q), 24.8 (q), 25.6 (q), 17.95 (s), -5.7 (q). (Found: C, 54.58; H, 8.39; N, 4.16%. $C_{15}H_{29}O_5N$ requires C, 54.38; H, 8.76; N, 4.23%).

L-Deoxymannojirimycin (18). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-L-mannonolactam (16) (100 mg, 0.3 mmol) was dissolved in dry tetrahydrofuran (5 ml) and stirred with borane:dimethylsulphide complex (90 µl, 0.9 mmol) under dry nitrogen for 4 h when TLC (ethyl acetate) showed no starting material (R_f 0.5) and one major product (R_f 0.9). The reaction was quenched with saturated sodium sulphate and the two phases separated. The aqueous phase was extracted with dichloromethane (3 x 5 ml) and the organic phases were combined, dried (magnesium

sulphate) and the solvent removed under reduced pressure. The residue was dissolved in trifluoroacetic acid/water (1:1, 5 ml) and left to stand for 2 h when TLC (ethanol/chloroform/ammonia, 45/45/10) revealed one product (R_f 0.1). The solvent was removed under reduced pressure, and toluene (3 x 5 ml) was distilled from the residue. The product was purified by ion exchange chromatography to yield the title compound as a colourless oil. Treatment with aqueous hydrochloric acid (0.5M) and further purification by recrystallisation from methanol yielded L-deoxymannojirimycin (18), as the hydrochloride salt, (41 mg, 72%), m.p. 185°-187°C, $[\alpha]_D^{20}$ +10.2° (c, 0.37 in water). m/z (CI NH_3); 164 ($M+H^+$, 100%), 128, 110. δ_H (D_2O); 4.10 (1H, ddd, H-2), 3.72 (1H, dd, H-4), 3.69 (1H, dd, H-6), 3.54 (1H, dd, H-3), 3.27 (1H, dd, H-1'), 3.10 (1H, dd, H-1), 3.01 (1H, ddd, H-5). δ_C (D_2O); 73.1 (d, C-2), 66.6 (d), 66.5 (d), 61.1 (d, C-5), 58.8 (t, C-6), 48.3 (t, C-1).

L-Mannono-δ-lactam (17). 6-O-tert-Butyldimethylsilyl-2,3-O-isopropylidene-L-mannono-δ-lactam (16) (66 mg, 0.2 mmol) was dissolved in trifluoroacetic acid/water (1:1, 5 ml) and left to stand for 1 h when TLC (10% methanol in chloroform) revealed no starting material (R_f 0.5) and TLC (2:1 chloroform/methanol) revealed one product (R_f 0.5). The solvent was removed under reduced pressure and toluene (3 x 5 ml) was distilled from the residue. Trituration with ether gave a white crystalline solid which was recrystallised from methanol to give L-mannono-δ-lactam (17), (32mg, 91%), m.p. 165°-170°C, $[\alpha]_D^{20}$ -2.0° (c, 1.0 in water). m/z (DCI NH_3); 178 ($M+H^+$, 100%), 112. δ_H (D_2O); 4.16 (1H, d, H-2), 3.83 (1H, dd, H-3), 3.68 (1H, dd, H-4), 3.54 (2H, m, H-6 and H-6'), 3.19 (1H, m, H-5). δ_C (D_2O); 173.5 (s, C-1), 71.9 (d, C-3), 68.2 (d, C-2), 67.1 (d, C-4), 61.1 (t, C-6), 57.3 (d, C-5).

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