Tetrahedron Letters,Vol.29,No.23,pp 2871-2874,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SHORT SYNTHESES OF D-DEOXYMANNOJIRIMYCIN AND D-MANNONOLACTAM FROM L-GULONOLACTONE AND OF L-DEOXYMANNOJIRIMYCIN AND L-MANNONOLACTAM FROM D-GULONOLACTONE

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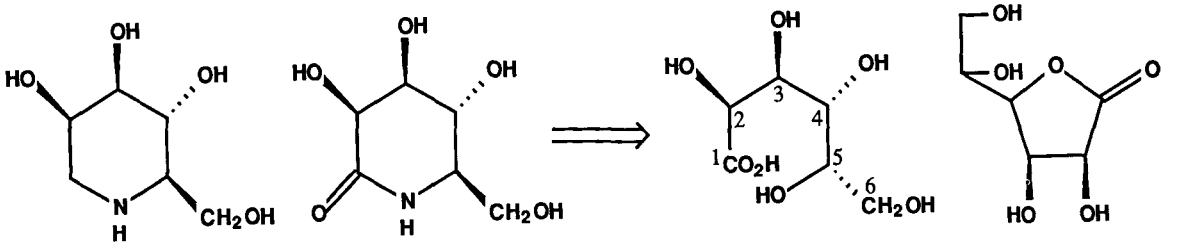
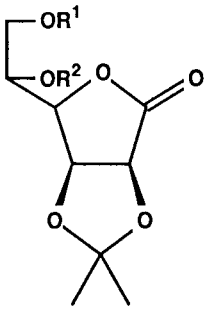
Short syntheses of D-deoxymannojirimycin and of D-mannonolactam from L-gulonolactone are reported; identical sequences on D-gulonolactone lead to L-deoxymannojirimycin and L-mannonolactam.

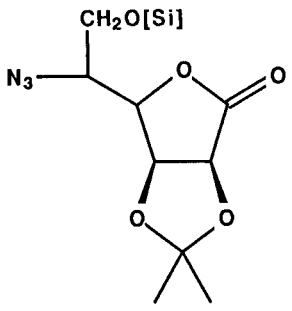
Swainsonine, isolated from Astragalus and Swainsona species and from Metarhizium anisopliae, is an inhibitor of mannosidase II of glycoprotein processing[1,2] and has potential as an agent for the stimulation of the immune response[3] and for the prevention of the metastasis of cancer.[4] Deoxymannojirimycin (1), isolated from Lonchocarpus sericeus,[5] inhibits glycoprotein processing mannosidase I[6,7] and a bovine α-L-fucosidase.[8] D-Mannonolactam (2), previously obtained by microbiological oxidation of nojirimycin B, is a powerful inhibitor of rat epididymal α-mannosidase and of apricot ß-glucosidase.[9]

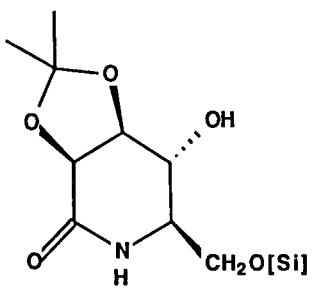
Deoxymannojirimycin (1) has been prepared using sequences which involve introduction of nitrogen either with retention of configuration at C-5 of D-mannose [10,11] or with inversion of configuration at C-2 of D-glucose.[11,12] Almost all these syntheses involve a significant amount of protection and deprotection of the carbohydrate and are not readily adaptable to the convenient preparation of larger amounts of material. Sugar lactones have considerable potential for short sequences for the preparation of polyhydroxylated pyrrolidines,[13] piperidines and octahydroindolizines in which the need for protecting groups is minimised. This paper reports a six-step synthesis of deoxymannojirimycin (1) and a five-step synthesis of mannonolactam (2) from 2,3-O-isopropylidene-L-gulonolactone (4); the preparations of L-deoxymannojirimycin and of L-mannonolactam from D-gulonolactone are also described.

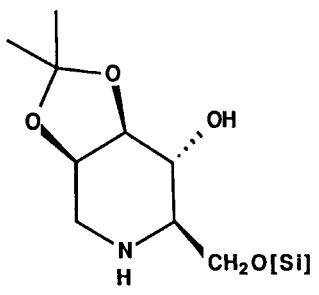
The synthesis of deoxymannojirimycin (1) and of the mannonolactam (2) from a derivative of L-gulonic acid requires introduction of nitrogen with inversion of configuration at C-5, and the linking of C-1 and C-5 by nitrogen; L-gulonolactone (3) is available commercially[14] or may readily be prepared by hydrogenation of either D-glucuronolactone[15] or vitamin C.[16]











(4) $R^1 = R^2 = H$
(5) R^1 = [Si] $R^2 = H$
(6) R^1 = [Si] $R^2 = SO_2CF_3$

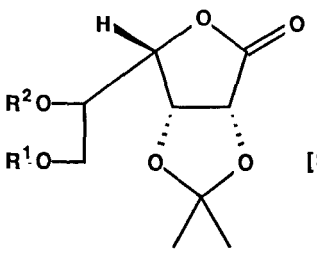
(7)

(8)

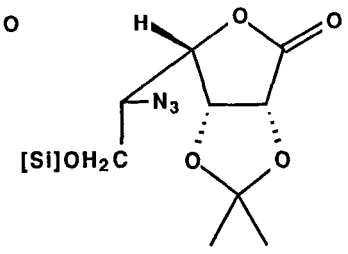
(9)

[Si] = $Me_2{}^tBuSi$

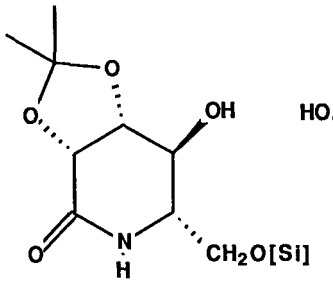
Treatment of L-gulonolactone (3) with acetone/dimethoxypropane in the presence of a catalytic amount of p-toluenesulphonic acid gave 2,3;5,6-di-O-isopropylidene-L- gulonolactone[17] [84% yield] which on selective hydrolysis with aqueous acetic acid afforded the diol (4),[18] m.p. 138°-141°C, $[\alpha]_D^{20}$ +82.2° (c, 1.0 in acetone), in 75% yield. The primary hydroxyl group was selectivly protected by reaction of (4) with tert-butylchlorodimethylsilane and imidazole in dimethyl formamide at -30°C to give the silyl ether (5) in 82% yield. Esterification of the remaining free hydroxyl group in (5) with trifluoromethanesulphonic anhydride and pyridine in dichloromethane at -40°C gave the triflate (6) which on reaction with sodium azide in dimethyl formamide formed the protected 5-azido-5-deoxy-D-mannonolactone (7), m.p. 86°-87°C, $[\alpha]_D^{20}$ -9.2° (c, 0.5 in $CHCl_3$) [83% yield from (5)]. Hydrogenation of the azide (7) in the presence of 10% palladium on carbon in methanol produced an amine which spontaneously underwent rearrangement to the δ-lactam (8), m.p. 104°-105°C, $[\alpha]_D^{20}$ +18.7° (c, 1.0 in $CHCl_3$) in 80% yield. Reduction of the lactam (8) with borane:dimethylsulphide in tetrahydrofuran at room temperature for 4 h gave the corresponding amine (9) which with aqueous trifluoroacetic acid at room temperature gave deoxymannojirimycin (1) in 84% yield [28% overall yield from 2,3-O-isopropylidene-L-gulonolactone]. The proton and carbon-13 NMR spectra and the mass spectra of both D-deoxymannojirimycin (1) and the hydrochloride of D-deoxymannojirimycin, m.p. 175°-180°C, $[\alpha]_D^{20}$ -10.9° (c, 0.3 in water), were identical to those of authentic samples of the free base (1) and of deoxymannojirimycin hydrochloride, respectively.[12] Hydrolysis of the protected lactam (8) with aqueous trifluoroacetic acid at room temperature gave D-mannonolactam (8), m.p. 168°-170°C, $[\alpha]_D^{20}$ +2.3° (c, 1.0 in water) [lit.[9] m.p. 169°-170°C, $[\alpha]_D^{20}$ +1.6° (c, 1.0 in water)] in 77% yield [26% overall yield from 2,3-O-isopropylidene-D-gulonolactone].



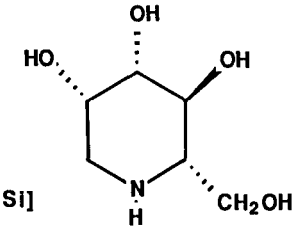
(10) $R^1 = R^2 = H$
(11) $R^1 = [Si]$ $R^2 = H$
(12) $R^1 = [Si]$ $R^2 = SO_2CF_3$



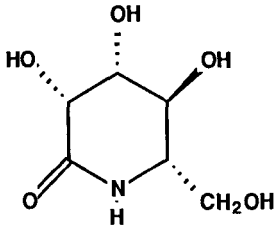
(13)



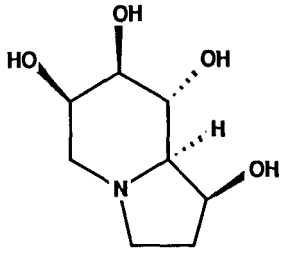
(14)



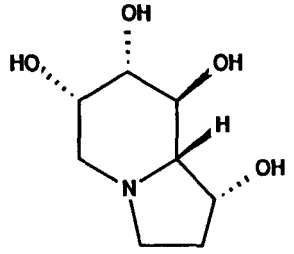
(15)



(16)



(17)



(18)

D-Gulonolactone is also readily available[14] and by an identical sequence to that above allows the synthesis of L-deoxymannojirimycin (15) and of L-mannonolactam (16). Thus, D-gulonolactone was converted[19] into 2,3-O-isopropylidene-D-gulonolactone (10), m.p. 139°-141°C $[\alpha]_D^{20}$ -79.4° (c, 1.0 in acetone) [lit.[20] m.p. 142°-143°C $[\alpha]_D^{20}$ -76.5° (c, 2.8 in acetone)] in 65% yield. Selective silylation of the primary alcohol function in (10) gave the silyl ether (11) in 79% yield. Formation of the triflate (12), followed by reaction with sodium azide gave the protected azido-L-mannonolactone (13), m.p. 86°-87°C, $[\alpha]_D^{20}$ +8.6° (c, 1.1 in $CHCl_3$) [72% yield from (11)]. Hydrogenation of the azide (13) afforded the lactam (14), m.p. 104°-105°C, $[\alpha]_D^{20}$ -17.9° (c, 0.86 in $CHCl_3$) in 76% yield. Reaction of the lactam (14) with borane:dimethylsulphide, followed by hydrolysis of the resulting amine with aqueous trifluoroacetic acid, led to the formation of L-deoxymannojirimycin (15) in 72% yield [31% overall yield from 2,3-O-isopropylidene-D-gulonolactone (10)]. The proton and carbon-13 NMR spectra and the mass spectra of both L-deoxymannojirimycin (15) and the hydrochloride of L-deoxymannojirimycin (15), m.p. 174°-179°C, $[\alpha]_D^{20}$ +12.6° (c, 0.5 in water), were identical to those of authentic D-deoxymannojirimycin (1) and the corresponding hydrochloride.[12] Hydrolysis of the protected lactam (14) with aqueous trifluoroacetic acid at room temperature gave L-mannonolactam (16), m.p. 165°-170°C, $[\alpha]_D^{20}$ -1.0° (c, 0.25 in water) in 82% yield [36% overall yield from 2,3-O-isopropylidene-D-gulonolactone].

Recently, a novel indolizidine alkaloid 6-epicastanospermine was isolated from Castanospermum australe and on the basis of spectroscopic evidence was assigned the structure (17);[21] however, an enantiospecific synthesis of (17) indicated that the natural product has the opposite absolute configuration and therefore has the structure (18).[22] The easily prepared protected enantiomeric lactams (8) and (14) should be suitable intermediates for the syntheses of (17) and (18) respectively.

In summary, this paper reports short syntheses of deoxymannojirimycin and of mannonolactam from L-gulonolactone; the first syntheses of L-deoxymannojirimycin and of L-mannonolactam are also described. A comparison of the inhibition of glycosidases by these compounds will be reported elsewhere.[23]

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23. Support for this work from SERC (for a graduate studentship to NGR) and from G. D. Searle is gratefully acknowledged.

(Received in UK 28 March 1988)