New Synthesis of (+)- and (−)-Nojirimycin from *myo*-Inositol

Noritaka Chida, Yuka Furuno, and Seiichiro Ogawa*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama, 223 Japan

A report of a new synthesis of nojirimycin (**1a**), as well as its antipode (**1b**), from optically active seven-membered hemiacetal lactones (**2a,b**) derived from *myo*-inositol by a five step reaction; the hydrogen sulphite adduct of (**1b**) shows high inhibitory activity against β-glucosidase and α-mannosidase, being almost comparable to that of mannojirimycin.

Nojirimycin[1] and mannojirimycin[2] (nojirimycin B), produced by *Streptomyces lavendulae* SF-425, show a potent inhibitory activity against glucosidases and glucoamylase.[3] In particular, much attention has been focused on the corresponding 1-deoxy analogues,[4,5] the inhibitors of trimming glycosidase,[6] which have been shown to interfere with HIV-induced syncytium formation and viral infectivity.[7] Recently, therefore, interest in the structure and enzyme-inhibitory activity relationship and chemical modification[8] of these compounds has increased.

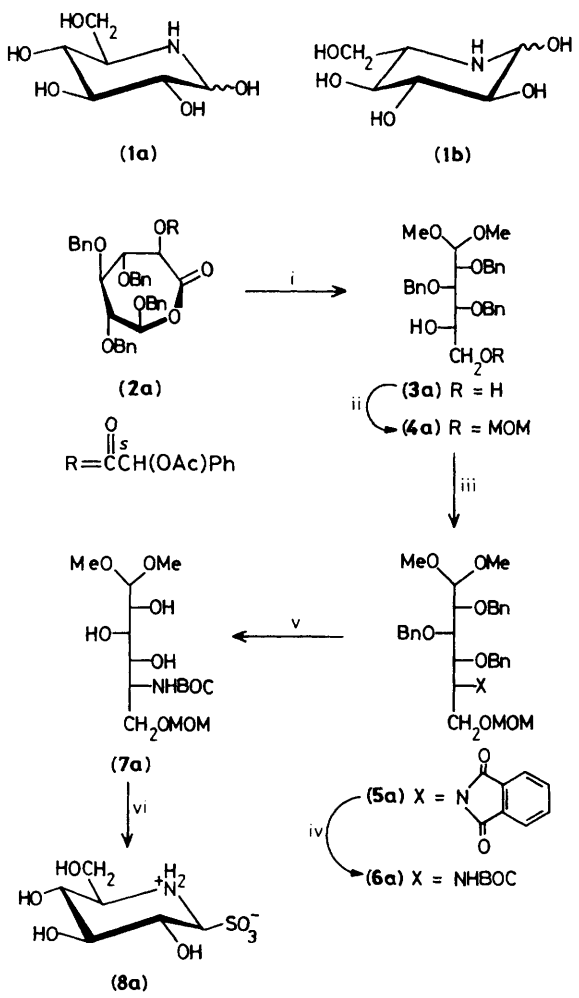
Synthesis of nojirimycin has been achieved successfully by several groups starting from D-glucose[1,9] and L-tartaric acid.[10] However, as yet its enantiomer has not been synthesized. We describe herein a new synthesis of (+)-(**1a**) and (−)-nojirimycin (**1b**) from *myo*-inositol *via* the optically active, seven-membered hemiacetal lactones (**2a,b**),[11] together with the inhibitory activity of (**1b**).

Treatment of compound (**2a**) with trimethyl orthoformate in methanol in the presence of toluene-*p*-sulphonic acid (reflux, 40 min), and successive reduction with lithium aluminum hydride in tetrahydrofuran (THF), afforded 2,3,4-tri-*O*-benzyl-L-idose dimethyl acetal (**3a**) in 74% yield. The primary hydroxy group was protected with the methoxymethyl group by treatment of (**3a**) with chloromethylmethylether and di-isopropylethylamine in CH_2Cl_2 (0 °C, 5 h), giving compound (**4a**) in 79% yield. The Mitsunobu reaction[12] of (**4a**) with phthalimide in THF was carried out successfully to introduce the phthalimido function at C-5 *via* S_N2 reaction, giving mainly compound (**5a**) in 75% yield. Removal of the phthaloyl group of (**5a**) was effected by treatment with hydrazine in methanol and the resulting amine was successively converted into the *N*-t-butoxycarbonyl derivative (**6a**) in 74% yield. Hydrogenolysis of (**6a**) in ethanol in the presence of $Pd(OH)_2$ on carbon gave quantitatively the trihydroxy compound (**7a**), an aqueous solution of which was treated with sulphur dioxide at 40 °C to give, after 3 days, the crystalline

Table 1. Inhibitory activity of the hydrogen sulphite adducts against three enzymes.

Compounds	α-Glucosidase[a]	β-Glucosidase[b]	α-Mannosidase[c]
Nojirimycin hydrogen sulphite adduct	77.4 (14.5)[d]	89.6 (8.0)	9.4 (>100)
Mannojirimycin hydrogen sulphite adduct	1.3 (>100)	98.0 (4.4)	55.5 (84.0)
(**8a**)	76.1 (17.0)	85.8 (9.4)	11.7 (>100)
(**8b**)	2.1 (>100)	91.7 (4.5)	31.2 (>100)

[a] Yeast α-glucosidase, *p*-nitrophenyl-α-D-glucopyranoside (0.66 mM), PBS (100 mM), pH 6.8. [b] Almonds β-glucosidase, *p*-nitrophenyl-β-D-glucopyranoside (0.33 mM), acetate buffer (100 mM), pH 5.0. [c] Jack bean α-mannosidase, *p*-nitrophenyl-α-mannopyranoside (20 mM), acetate buffer (100 mM), pH 4.5. [d] Inhibition (*I*%) determined at the final concentration of 100 μg/ml; numbers in the parentheses denotes IC_{50} (concentrations required to cause 50% inhibition, μg/ml) values.



Scheme 1. For convenience, only single enantiomers [(**3**)—(**8**)] corresponding to (+)-nojirimycin (a series) are depicted. *Reagents and conditions:* i, $CH(OMe)_3$, TsOH (Ts = $OSO_2C_6H_4Me$), MeOH, 70 °C, then $LiAlH_4$, THF, 0 °C; ii, MOMCl, $(Pr^i)_2NEt$, CH_2Cl_2, 0 °C; iii, phthalimide, Ph_3P, diethylazodicarboxylate, THF, room temp.; iv, $H_2NNH_2{\cdot}H_2O$, MeOH, reflux, then $(BOC)_2O$, Et_3N, CH_2Cl_2, room temp.; v, H_2, 20% $Pd(OH)_2$, EtOH; vi, SO_2 gas, H_2O, 0—40 °C, 3 days.

hydrogen sulphite adduct (**8a**) (58% yield) whose ^1H and ^{13}C n.m.r. (D_2O) and i.r. (KBr) spectra were superimposable on those of an authentic sample.[1] The adduct was treated with Dowex 1 × 2 (OH^-) resin to give the free base (**1a**), $[\alpha]_D^{23}$ + 74° (H_2O) [lit.[1] $[\alpha]_D^{24}$ + 71° (H_2O)].

Similarly, starting from the lactone (**2b**), (−)-nojirimycin (**1b**), $[\alpha]_D^{20}$ −74° (H_2O), was synthesised, which was identical to (**1a**), except for the sign of the optical rotation.

Biological activity of the hydrogen sulphite adducts (**8a,b**) of synthetic (**1a,b**), and authentic samples of (**1a**) and mannojirimycin are shown in Table 1. Although nojirimycin hydrogen sulphite adducts show somewhat different inhibitory activity[13] compared to their parent free nojirimycins, its chemical stability allowed us to compare and evaluate their activity accurately. Judging from the activity of (**8b**), the synthetic (−)-nojirimycin (**1b**) would conceivably possess high inhibitory activity against β-glucosidase as well as α-mannosidase, almost comparable to mannojirimycin, being rather different from its antipode.

The inhibitory activity of (**1b**) itself, and of the antipodes of mannojirimycin and the corresponding 1-deoxy derivative now become of interest.

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