PRACTICAL SYNTHESIS OF NOJIRIMYCIN[1]

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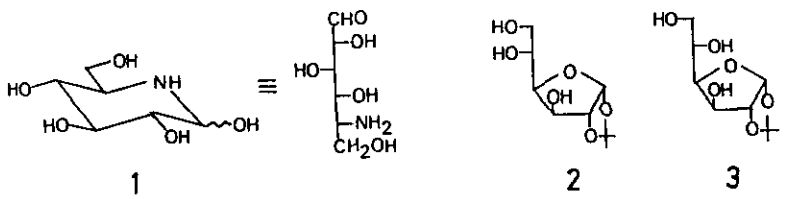
Abstract——The short step and efficient synthesis of nojirimycin (**1**) from commercially available 1,2-isopropylidene-D-glucofuranose (**2**) was described. Oxidation of **2** with $(Bu_3Sn)_2O$-Br_2 followed by oximation, isomerization, and stereoselective reduction gave the 5-amino derivative of gluco-configuration (**6a**), which was converted to nojirimycin bisulfite adduct (**8**) in 50% overall isolated yield.

Nojirimycin, 5-amino-5-deoxy-D-glucose (**1**), is the compound of biological interest as a glucosidase inhibitor.[3] One of the logical entry for the synthesis of **1** is that to convert the 5-hydroxyl group in D-glucose into an amino group. Among several syntheses so far appeared,[4,5] some utilize the glucofuranose derivatives[4] by following this idea. However, the several additional steps required for protection and deprotection of the extra hydroxyl groups are reducing the value of these syntheses.

We thought that the above requirement can be simply achieved by a regioselective oxidation of C5-hydroxyl group of commercially available 1,2-isopropylidene-D-glucofuranose (**2**), followed by an oximation and the stereoselective reduction of the resulting oxime, without protection of the other hydroxyl groups. This was verified as follows.



1 2 3

Chart 1

Application of the mono-oxidation method by bis-tributyltin oxide and bromine[6] to **2** gave the crystalline 5-oxo derivative (**4**),[7] mp 108-110°C, in 92 % yield. The position of oxidation was proved by hydride reduction of **4** to the original glucofuranose (**2**) and the idofuranose (**3**). Treatment of **4** with O-methylhydroxylamine hydrochloride in the presence of $NaHCO_3$ gave two O-methyloximes, **5a** (mp 74-76°C) and **5b** (oil), in a ratio of 1:2.5. On the other hand, a similar oximation in the presence of 5 eq. mol of Na_2CO_3 gave **5a** and **5b** in a ratio of 1.6:1. The both oximes gave the same equilibrium mixture (**5a**/**5b**=1:3.5), on treatment with a catalytic amount of p-TsOH in methanol, indicating that **5a** is a kinetic and **5b** is a thermodynamic product. Their configurations were determined by the X-ray analysis of the crystalline isomer **5a** (Fig. 1).[8] Since **5a** was shown as the E-isomer, **5b** must be the Z-isomer.

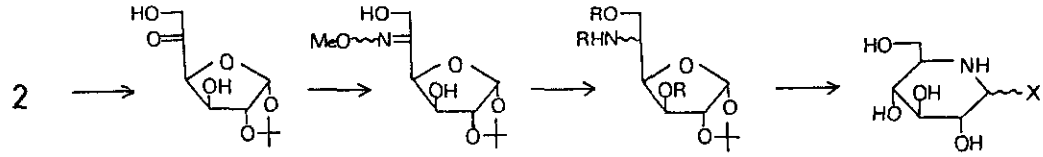


Chart 2

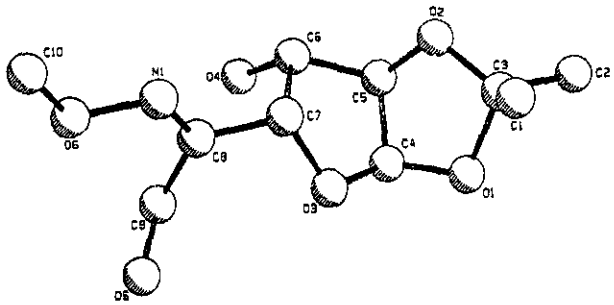


Fig. 1. The Crystal Structure of 5a

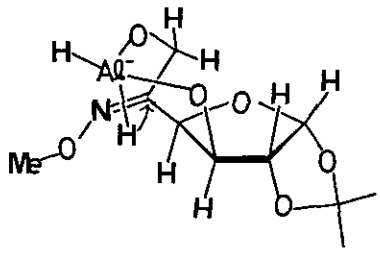


Fig. 2

Table I. Stereoselectivity in Redution of E- and Z-Oximes. A gluco(**6a**)/ido(**6b**) Ratio in The Products.*

Oxime	Reducing Agent					
	$Me_2S.BH_3$	LAH/ether	LAH/THF	LAH/DME	AlH_3/THF	H_2/Raney Ni
5a(E)	1.0	0.33	0.45	1.0	0.43	---
5b(Z)	1.0	1.5	1.0	3.0	4.0	1.7

* The ratio was determined by GLC of the corresponding triacetates.

Each oxime was reduced in a stereospecific manner to give the 5-amino derivative of gluco or ido configuration depending on both the stereochemistry of oximes and the nature of reducing agents. The results are summarized in Table I. Particularly, reductin of **5b** with AlH_3 gave the gluco-isomer (**6a**) over the ido-isomer (**6b**) in a 4:1 stereoselectivity, while redution of **5a** with LAH in ether gave the ido-isomer (**6b**) 3 times over the gluco-isomer (**6a**). This high gluco-selectivity in the reduction of the Z-isomer **5b** may be explained by an intramolecular hydride attack from the aluminum chelated species adopting the most stable conformation as depicted in Fig. 2.

The configurations of **6a** and **6b** were determined as follows. i) **6a** gave a positive Cotton effect in CD at 310 nm when measured in the presence of salicylaldehyde,[4a] ii) the derived triacetate **7a**, mp 150-151°C, gave the smaller retention time in GLC than the isomer **7b**, mp 92-96°C, in accordance with the relative mobilities of the triacetates of 1,2-isopropylidene-D-gluco- and -L-ido-furanose, and finally iii) **6a** was tranformed into nojirimycin.

Since a high yield transformation of the amine (**6a**) to nojirimycin (**1**) via the bisulfite adduct (**8**)[9] is already known,[4a] the present investigation opened a practical route to nojirimycin (**1**) from 1,2-O-isopropylidene-D-glucofuranose (**2**) without chromatographical separation of the stereoisomers at any stages. The following is a typical example.

Dried 1,2-isopropylidene-D-glucofuranose (**2**)(1 g), $(Bu_3Sn)_2O$ (5.5 g), and an excess of molecular sieves 3A in chloroform (30 ml) were heated under reflux until the glucoside dissolved completely. To this mixture, bromine (0.6 ml) was added at 0°C with stirring until the solution was faintly colored (5 min required), then the mixture was poured onto a column of silica gel. The column was washed throughly with chloroform, then eluted with AcOEt to yield the 5-oxo dreivative (910 mg, 92%). This was heated with O-methylhydroxylamine hydrochloride (526 mg) and $NaHCO_3$ (526 mg) in methanol (25 ml) for 1 h. The solvent was evaporated and the residue in EtOAc was passed through a short silica gel column to remove inorganic materials. The resulting O-methyloxime (1.02 g, Z/E ratio 2:1) was treated with a catalytic amount of p-TsOH in methanol for 2 h at room temperature. Evaporation of the solvent and removal of the catalyst by chromatography gave a gum (873 mg, Z/E ratio 3.5:1), which was treated with 5 mol eq. of $LiAlH_4$ in

dimethoxyethane (30 ml) for 5 h under reflux. The product was purified from inorganic materials by passing through a short silica gel column in chloroform-methanol (4:1-1:1) to give the 5-amino derivative (650 mg, 84%, gluco/ido ratio 2:1 determined by GLC as the triacetate). A portion of this (268 mg) was dissolved in water (3 ml) saturated with SO_2 and kept at room temperature for 3 days. Addition of methanol (10 ml) to the solution deposited crystals (160 mg) of nojirimycin bisulsite adduct (**8**) which was enough pure as judged from the mp (138-139°C) and the IR spectrum (identical with the reported spectrum[4a]). The overall yield was 50%. This is quantitatively interconvertible to nojirimycin (**1**).[4a]

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7. This compound was once prepared in very poor yield as an amorphous mass [O. Theander, Acta Chem. Scand., 1963, 17, 1751].
8. The X-ray analysis showed that **5a** exists in two different conformations in a crystalline state. Details will be reported in a full publication.
9. The β-configuration of the SO_3H group has been indicated by an X-ray analysis (Y. Kodama, T. Tsuruoka, T. Niwa, and S. Inouye, J. Antibiotics, 1985, 38, 116).

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