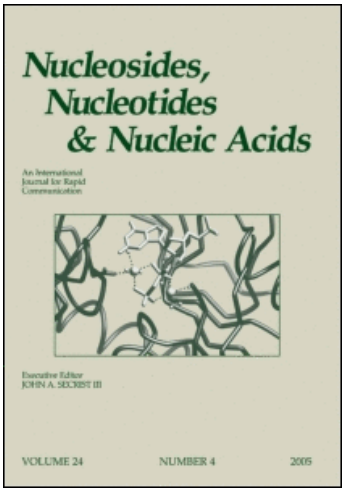

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C-Nucleoside Analogues of Nicotinamide Mononucleotide (NMN)

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C-NUCLEOSIDE ANALOGUES OF NICOTINAMIDE MONONUCLEOTIDE (NMN).

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ABSTRACT

5-(β-D-Ribofuranosyl)nicotinamide (**IIc**) and 6-(β-D-ribofuranosyl)picolinamide (**IId**) and their corresponding α-isomers (**III**) were synthesized from ribonolactone. The C-nucleoside **IIc** was further converted to its 5'-monophosphate **IIp** which is isosteric to NMN (**Ip**).

We reported the synthesis of 5-(β-D-ribofuranosyl)nicotinamide (**IIc**) and its N-methylated derivative, from 2,4:3,5-di-O-benzylidene-D-aldehydoribose, as the C-nucleoside analogues isosteric and isoelectronic to nicotinamide riboside (**I**, Figure 1).[1] Similar synthesis of several 2-D-ribofuranosylpyridines were also reported.[2] These synthetic procedures which require preparation of the aldehydoribose are not amenable for large-scale preparations.

In order to prepare **IIc** more efficiently, we investigated a new approach starting from the commercially available D-ribonolactone[3] (**1**, Scheme 1). 2,3-O-Isopropylidene-5-O-(tert-butyldimethyl)silyl-D-ribonolactone (**2**)[4] was prepared in two steps from **1**. Upon reaction of **2** with 3-cyano-5-lithiopyridine, 1-(3-

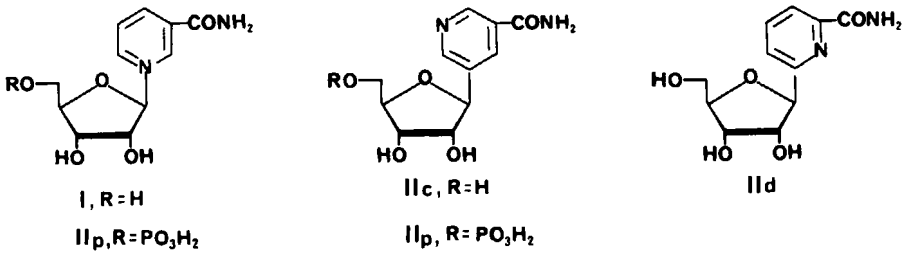
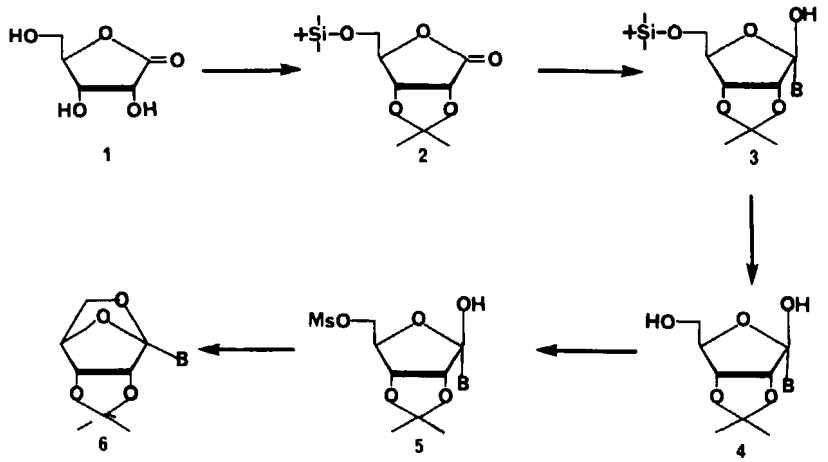
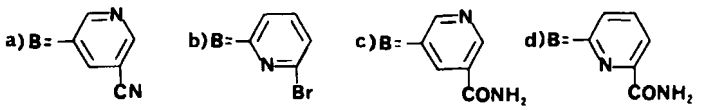


Fig.1





Scheme 1

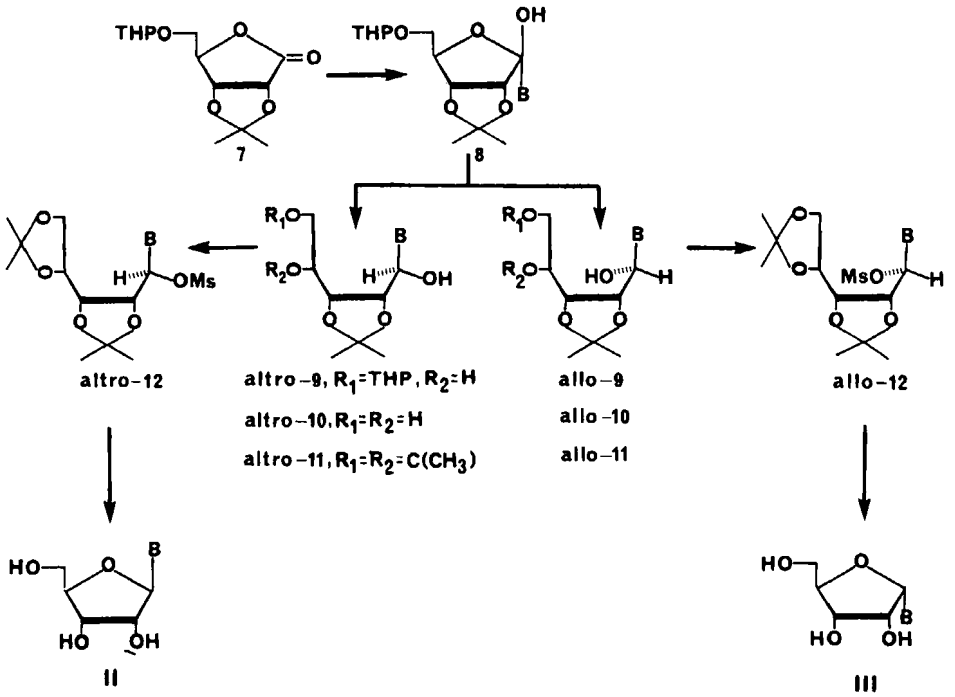
cyanopyridin-5-yl)-2,3-O-isopropylidene-5-O-(tert-butyldimethyl)-silyl-β-D-ribo-furanose (**3a**) was obtained in 79% yield as the sole product. The anomeric configuration of **3a** was established by the following: Desilylation of **3a** with Et_3NHF to **4a** followed by mesylation afforded the mesylate **5a** which was converted in high yield into the 1,5-anhydro derivative **6a** by treatment with DBU in CH_2Cl_2.

Addition of 3-cyano-5-lithiopyridine with 2,3-O-isopropylidene-5-O-tetrahydropyranyl-D-ribonolactone (**7**)[3] afforded a

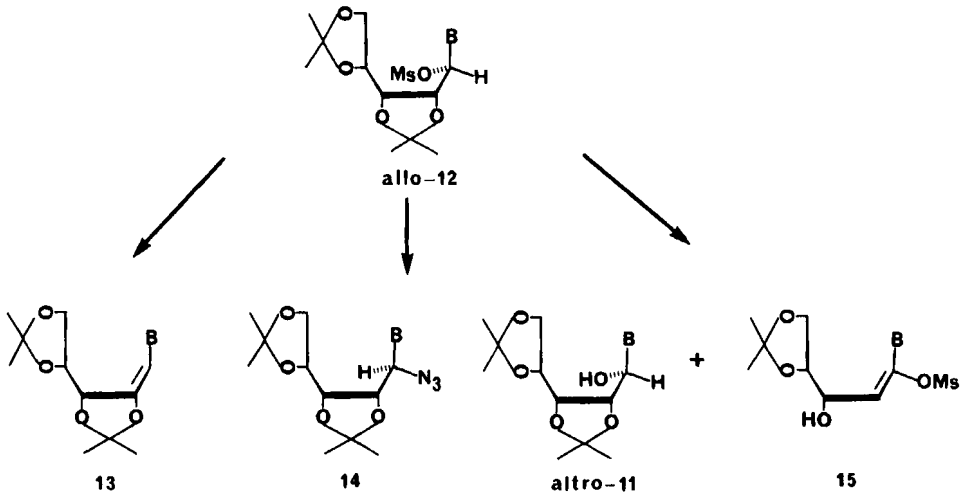
diasteromeric mixture of **8a**. Treatment of **8a** with $NaBH_4$ afforded a mixture **9a** (Scheme 2) of the allo and altro isomers in about 1:1 ratio. After separation of these epimers on a silica gel column, each isomer was separately treated with TsOH/MeOH to **10a** and then with acetone/TsOH to give the respective 2,3:4,5-di-O-isopropylidene derivative **11a** which was mesylated to **12a**. Solvolysis of allo-**12a** with trifluoroacetic acid in CH_2Cl_2 afforded exclusively the α-C-nucleoside **IIIa**. Similarly, altro-**12a** was exclusively converted into the β-C-nucleoside **IIa**.

In the same series of reactions of **7** with 2-bromo-6-lithiopyridine, similar results were obtained (Scheme 2). The major difference between the two pyridine derivatives was the allo-altro ratio in the product of $NaBH_4$ reduction of the pyridinyl-β-D-ribose. 1-(2-Bromopyridin-6-yl)-β-D-ribofuranose (**8b**) gave a 4:1 allo/altro mixture **9b**. Conversion of the 2-bromo or 3-cyano substituent into carboxamide function was performed by the reported procedure.[1]

This approach to the synthesis of **IId**, however, was very unsatisfactory, since only one fifth of **9b** gives the β-C-nucleoside. We, therefore, investigated the possibility to convert the allo isomer **9** into the altro counterpart. Attempts at nucleophilic displacement of the mesyl group in allo-**12b** with ^-OAc resulted in the formation of 1,2-olefin **13b** (Scheme 3). Treatment of allo-**12b** with a better nucleophile $^-N_3$, however, afforded the 1'-azido derivative **14** in good yield, suggesting that the mesyl group in **12b** could be replaceable with a potent oxygen nucleophile. Actually, when allo-**12b** was treated with potassium superoxide (KO_2) and 18-crown-6, accoding to the procedure of Corey et al.,[5] afforded altro-**11b** together with the new olefin **15**. Although the yield of conversion from allo-**12b** to altro-**11b** was low (24%), this represents the first example of the synthesis of β-C-nucleoside from the allo intermediate. Phosphorylation of



Scheme 2



Scheme 3

IIc by the Yoshikawa procedure[6] modified by Marquez et al.[7] with $POCl_3$ in trimethyl phosphate afforded the C-nucleotide analogue of NMN.

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REFERENCES

1. Kabat, M. M., Pankiewicz, K. W., Watanabe, K. A. (1987) J. Med. Chem., 30, 924.

2. Belmans, M., Vrijens, I., Esmans, E. L., Lepoivre, J. A., Alderweireldt, F. C., Wotring, L. L., Townsend, L. B. (1987) Nucleosides Nucleostides, 6, 245.

3. Reaction of a sugar lactone with lithiopyridine was first reported by Ogura et al.: Ogura, H., Takahashi, H., Itoh, T. (1972) J. Org. Chem., 37, 72: Ogura, H., Takahashi, H. (1974) J. Org. Chem., 39, 1374.

4. Wilcox, C. S., Long, G. W., Suh, H. (1984) Tetrahedron Lett., 25, 395.

5. Corey, E. J., Nicolaon, K. S., Shibasaki, M., Machida, Y., Shiner, C. S. (1975) Tetrahedron Lett., 3183.

6. Yoshikawa, M., Kato, T., Takenishi, T. (1967) Tetrahedron Lett., 5065.

7. Gebeyehu, G., Marquez, V. E., Kelly, J. A., Cooney, D. A., Jayaram, H. N., Johns, D. G. (1983) J. Med. Chem., 26, 922.