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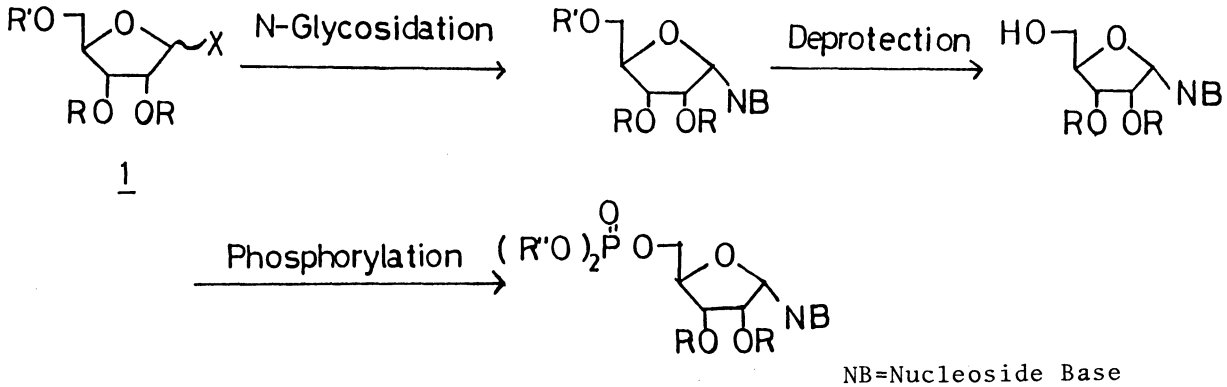
HIGHLY STEREOSELECTIVE SYNTHESIS OF α-RIBONUCLEOTIDES *VIA* A CYCLIC PHOSPHATE

Teruaki MUKAIYAMA, Yujiro HAYASHI, and Yukihiko HASHIMOTO
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Several α-ribonucleotides are conveniently synthesized from the cyclic phosphate derivatives of ribose and nucleoside bases in highly stereoselective manner.

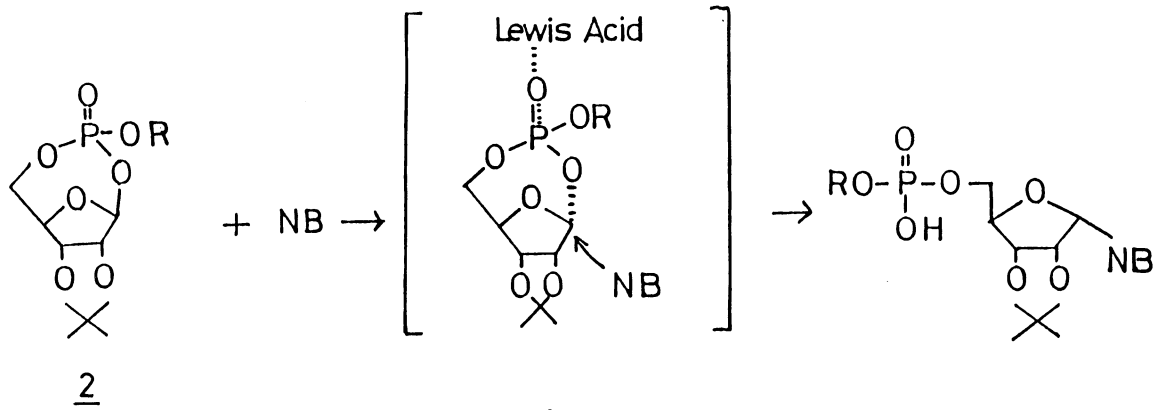
Recently a great progress has been attained in the field of nucleic acid chemistry. The active research has being done in the area of chemical synthesis of DNA and RNA as well as various biologically active nucleosides and nucleotides. In the synthetic field, however, stereoselective synthesis of 1',2'-*cis*-nucleosides still remains as one of the important research topics,[1] and there have been few general and useful methods reported for the synthesis of 1',2'-*cis*-nucleotides as yet. In this communication, we would like to report a highly stereoselective and one-step synthesis of α-ribonucleotides by using a cyclic phosphate derivative of ribose as a starting material.

Based on the conventional method for the synthesis of β-ribonucleotides, α-isomer is expected to be formed by the following reactions (Scheme 1), however, some troublesome problems are pointed out, namely, 1) three tedious steps are required, 2) several steps are also necessary for the preparation of the starting material 1, 3) the highly selective N-glycosidation for α-ribonucleosides is still a difficult problem as mentioned above. To overcome these problems, a starting glycosyl donor 2 was designed based on the following considerations; if the glycosidation reaction proceeds in the S_N2 fashion, an α-ribonucleotide is



Scheme 1.

expected to be formed in high stereoselectivity, because the phosphoryl group covers the β-face of the ribofuranose moiety (Scheme 2). Moreover, the desired nucleotide can be synthesized in one step to skip the conventional long tedious steps.



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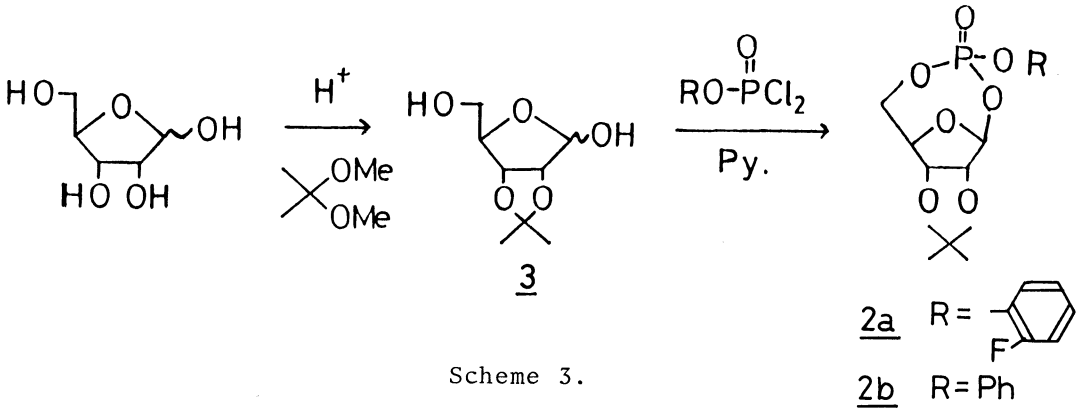
Scheme 2.

First, the preparation of the starting cyclic phosphate 2 was examined and a convenient preparative method was developed as shown in Scheme 3. The following is the procedure for the preparation of 2,3-O-isopropylidene-β-D-ribofuranose cyclic 1,5-(2-fluorophenyl)phosphate (2a): To a CH_2Cl_2 solution (180 ml) of 2,3-O-isopropylidene-D-ribofuranose (3)[2] (10 mmol) was added pyridine (2 ml) and a CH_2Cl_2 solution (20 ml) of 2-fluorophenyl phosphorodichloridate[3] (12 mmol) at 0 °C under an argon atmosphere. After the reaction was completed (0 °C, 12 h, then rt, 12 h), the solvent was removed in vacuo and the residue was purified by column chromatography to give 2a[4] (6.1 mmol) in 61% yield.



Scheme 3.

The reaction conditions, solvents, and activators (Lewis acids, such as $TiCl_4$, TMSOTf, $SnCl_4$, $ZnCl_2$, CuI, $SnCl_2$, $SnBr_2$, $AlMe_3$) were examined taking 5,6-dimethylbenzimidazole (4) as a model nucleoside base and 2,3-O-isopropylidene-β-D-ribofuranose cyclic 1,5-phenylphosphate (2b) as a starting material. Thus, it was found that THF and $SnBr_2$ are the most suitable solvent and activator[6] respectively. The ratio of the reactants influenced the yield, and the molar ratio, 2b : $SnBr_2$: 4 = 1 : 2 : 4, gave the best result (71% yield, α/β > 95/5).[7] The effect of the

substituent in phosphoryl group was examined and among various substituents screened (Et, Ph, 4-chlorophenyl, 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl), 2-fluorophenyl derivative gave the best result (81% yield). The typical reaction procedure is as follows: A hexane solution (0.54 ml) of *n*-BuLi (0.84 mmol) and $SnBr_2$ (113 mg, 0.41 mmol) were added successively to a THF solution (3 ml) of 5,6-dimethylbenzimidazole (4, 123 mg, 0.84 mmol) under an argon atmosphere at 0 °C. To this mixture was added a THF solution (3 ml) of cyclic phosphate 2a (68 mg, 0.20 mmol) at room temperature. The resulting mixture was stirred overnight and was quenched with triethylammonium hydrogencarbonate buffer (0.25 mol/l, pH 7.5). The resulting precipitate was filtered off through a celite pad, and the organic materials were extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 10 : 1 ⟶ $CHCl_3$: MeOH : NEt_3 = 10 : 1 : 1) to afford triethylammonium salt of 1-[5-O-(2-fluorophenyl)phosphono-2,3-O-isopropylidene-α-D-ribofuranosyl]-5,6-dimethylbenzimidazole[8] (95 mg, 81% yield, α/β > 95/5).

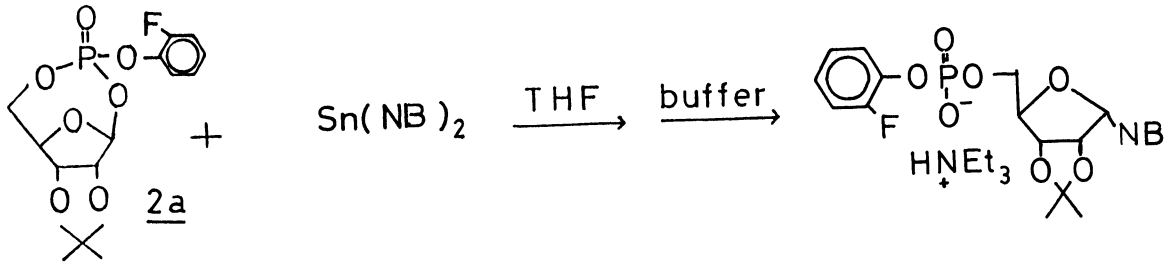
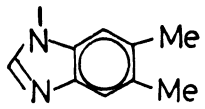
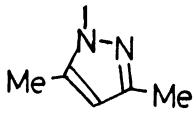
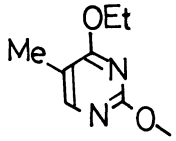
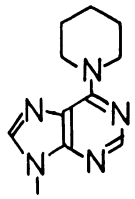


Table 1. Synthesis of α-nucleotides

NB	Yield / %	Conditions
	81	r.t., overnight[a]
	57	r.t., 2 d[a]
	60	r.t., 4 d[b]
	30	r.t., 4 d[a,c]

a) Only α-isomer is detectable by NMR spectroscopy.
b) The isomer ratio is 9:1. The major isomer is an O-glycosyl compound,[9] and the structure of the minor isomer is not determined.
c) *t*-BuOK and $LiClO_4$ are used instead of *n*-BuLi.

Under similar conditions, the reactions between 2a and various nucleoside bases were studied and the results are summarized in Table 1.

It is noted that the derivative of α-adenosine 5'-phosphate is easily synthesized in high stereoselectivity. Further, the present method has several unique characteristics which should be pointed out: contrary to the general synthetic methods of nucleotides, the phosphoryl group is introduced in the first step to play a role as 5'-phosphate substituent and also it behaves as a leaving group on the anomeric center by the attack of the nucleoside base to afford the corresponding α-nucleotide selectively.

An attempt to prepare 2'-deoxyribonucleotide by the same procedure is now in progress.

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References

1) T. Mukaiyama, Y. Hashimoto, Y. Hayashi, and S. Shoda, Chem. Lett., 1984, 557, and the references cited therein.

2) M. Kiso and A. Hasegawa, Carbohydr. Res., 52, 95 (1976).

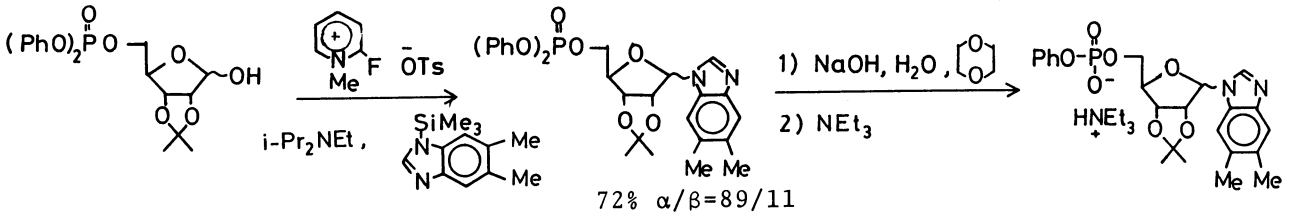
3) G. R. Owen and C. B. Reese, Synthesis, 1974, 704.

4) Diastereomer ratio was determined by NMR spectroscopy as 3.5:1, and one isomer[5] was obtained by the recrystalization from CH_2Cl_2-Et_2O, and it was used in the following reactions.

5) White crystal, mp 131.0-132.6°C, ^{31}P NMR ($CDCl_3$) δ=-4.980, ^1H NMR ($CDCl_3$) δ=1.3 (3H, s), 1.5 (3H, s), 4.1 (1H, ddd, J=29, 13, 1 Hz), 4.3-4.7 (3H, m), 4.8 (1H, d, J=5.4 Hz), 5.7 (1H, d, J=25.2 Hz), 7.0-7.4 (4H, m), MS, Found:m/e 346.0636. Calcd for $C_{14}H_{16}O_7PF$: M, 346.0617.

6) T. Miwa, K. Narasaka, and T. Mukaiyama, Chem. Lett., 1984, 1093.

7) Only one isomer was detectable by NMR spectroscopy, and it was assigned to be an α-isomer by the comparison with the authentic sample made by the following scheme.[1]



8) Oil, ^1H NMR ($CDCl_3$) δ=1.1 (9H, t, J=8 Hz), 1.1 (3H, s), 1.2 (3H, s), 2.2 (6H, s), 3.8 (6H, q, J=8 Hz), 3.9-4.1 (2H, m), 4.2-4.3 (1H, m), 4.5-4.8 (2H, m), 6.1 (1H, d, J=3.6 Hz), 6.6-7.0 (5H, m), 7.2 (1H, s), 7.8 (1H, s).

9) The structure was assigned by the UV spectroscopy; (C_2H_5OH) 262 nm (1.5×10^4). See E. Wittenburg, Chem. Ber., 99, 239 (1966).

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