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Synthesis of *C*-Ribo-nucleosides Having Typical Aromatic Heterocycles as Base Moiety

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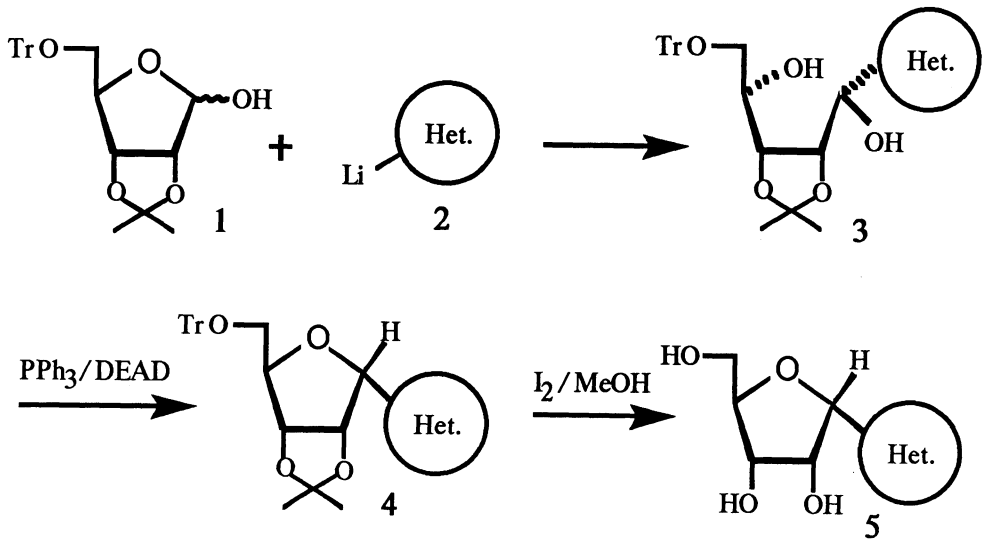
Some *C*-ribo-nucleosides having typical aromatic heterocycles as base moiety were synthesized from the stereoselective addition of lithium salt of aromatic heterocycles to the protected D-ribose followed by the stereospecific cyclization under Mitsunobu conditions.

Recently, natural and unnatural *C*-nucleosides have received considerable attention due to their marked antiviral and antitumor activities.[1] Generally, their synthetic methods require many steps and have much limitation to prepare many kinds of *C*-nucleosides. Therefore, our aim has been to develop synthetically useful methods of *C*-nucleosides.[2] As a part of this work, we intended to establish a synthetically simple method of *C*-ribo-nucleosides having typical π-excessive and π-deficient heterocycles as base moiety. Our preliminary procedure had the obstacles of both troublesome deprotection and difficult application to *N*-containing heterocycles.[3] Here we will present a synthetically useful and general method for the synthesis of *C*-ribo-nucleosides without the above drawbacks.



In the case of heteroatoms (O and S), the configuration of C-1' in 3 is *R*; in the case of heteroatom (N), the configuration of C-1' in 3 is *S*.

2,3-*O*-Isopropylidene-5-*O*-trityl-D-ribofuranose **1** was allowed to react with lithium salt of aromatic heterocycles **2** to give the corresponding D-ribofuranosyl heterocycles **3** in good yield and a stereoselective manner. Then **3** was cyclized in high yield and a stereospecific manner by the Mitsunobu conditions to afford the desired *C*-ribo-nucleosides **4**, which could be easily deprotected together with a small amount of epimers.

A typical procedure is shown in the following preparation of 2-(D-ribofuranosyl)thiophene **5c**. To a stirring mixture of thiophene (130 mg, 1.54 mmol) and dry THF (3 ml) was added dropwise 1.66 M ^{n}BuLi hexane solution (0.9 ml, 1.49 mmol) under argon atmosphere at 0 °C. Then the mixture was stirred for 30 min at room temperature. Thus obtained thiophenyllithium solution was dropped to a stirring mixture of **1** (209 mg, 0.48 mmol) and dry THF (3 ml) under argon atmosphere at 0 °C. After the reaction mixture was stirred for 40 min under the same conditions, it was quenched with water and extracted with chloroform. The extract was purified by preparative TLC on silica gel (eluent: ethyl acetate / hexane = 1 / 3) to give the corresponding 2-thienyl-D-ribose **3c** in 99% yield.

Table 1. Synthesis of *C*-Ribo-nucleoside

Entry	Het. Base Moiety	Isolated Yield %					
		3 (*R*/*S*)		**4** (α/β)		**5**	
1	2-Furyl	**3a**	97 (*R*)	**4a**	78 (α)	**5a**[6a)]	65
2	2-Benzofuryl	**3b**	87 (2 / 1)	**4b**	78 (2 / 1)	**5b**	66
3	2-Thienyl	**3c**	99 (4 / 3)	**4c**	79 (4 / 3)	**5c**[6b)]	66
4	2-Benzothienyl	**3d**	91 (5 / 7)	**4d**	71 (5 / 7)	**5d**	82
5	2-Indolyl	**3e**	83 (8 / 1)	**4e**	93 (1 / 8)	**5e**	67
6	2-Pyridyl	**3f**	58 (*S*)	**4f**	43 (α)	**5f**	62

Next, a mixture of **3c** (837 mg, 1.62 mmol), triphenylphosphine (1.07 g, 4.08 mmol), and dry THF (10 ml) was stirred for 15 min and then the THF solution of diethyl azodicarboxylate (DEAD, 620 mg, 3.56 mmol) was added dropwise to the mixture. After 2.5 h stirring, the reaction mixture was purified by column chromatography on silica gel

(eluent: ethyl acetate / hexane = 1 / 3) to give 2-(2,3-*O*-isopropylidene-5-*O*-trityl-*D*-ribofuranosyl)thiophene **4c** in 79% yield. The **4c** (100 mg, 0.2 mmol) was deprotected by stirring with I_2 (50 mg, 11 mmol) in methanol (15 ml) at room temperature.[4] Purification was carried out by preparative TLC on silica gel (eluent: chloroform / methanol = 9 / 1). Similarly, 2-indolyllithium[5] protected with carbon dioxide were used in entry 5. Pyridyllithium in entry 6 was prepared by the modified procedure of literature[6]. And **4f** was deprotected by the treatment with 0.1 N HCl-THF in the place of I_2-MeOH method (low yield).

Some *C*-ribo-nucleosides obtained by the present method are summarized in Table 1. Although **5a** and **5c** have been reported,[7] the other compounds **5** are new *C*-ribo-nucleosides. The structures of **3**, **4**, and **5** were determined by both NMR measurements (COSY and NOESY: 1'-H ⟷ 5'-H for α-form; 1'-H ⟷ 4'-H for β-form) and the chemical transformation (cyclization with treatment of methanesulfonyl chloride-pyridine: (*R*)-**3** gave α-**4**; (*S*)-**3** gave β-**4**). The separation of *R*- and *S*-**3** could be carried out easily by preparative TLC on silica gel except **3c**. However, α- and β-**4c** could be separated easily by the above method in entry 3. Further, the cyclization under Mitsunobu conditions[8] was found to be completely stereospecific *via* the oxyphosphonium intermediate of 1-OH in D-ribose (Table 2). Interestingly, in the cyclization of **3f**, 2-(2,3-*O*-isopropylidene-5-*O*-trityl-α-L-lyxofuranosyl)pyridine was obtained in 40% yield *via* the oxyphosphonium intermediate of 4-OH in D-ribose. The fact suggests the hydrogen bonding of 1-OH between nitrogen atom in pyridine. Then, by adding a small amount of *p*-toluenesulfonic acid, **4f** could be obtained in 43% together with 40% of lyxose type product.

Table 2. Conversion of **3** to **4** (yield %)

(*R*)-3a ⟶	α-4a (76)	(*S*)-3d ⟶	β-4d (73)
(*R*)-3b ⟶	α-4b (71)	(*R*)-3e ⟶	β-4e (90)
(*S*)-3b ⟶	β-4b (70)	(*S*)-3f ⟶	α-4f (41)
(*R*)-3d ⟶	α-4d (75)		

Finally, the following advantages are expected for the present method: (1) The position of glycosidation in aromatic heterocycles may be controlled by the lithium-halogen exchange of the corresponding halogenated heterocycles. (2) Many kinds of sugar moieties may be applicable. Further investigation is undergoing in this laboratory.

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