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Synthesis of *C*-Nucleosides *via* [2+4]Cycloaddition of Ketene Intermediate[1]

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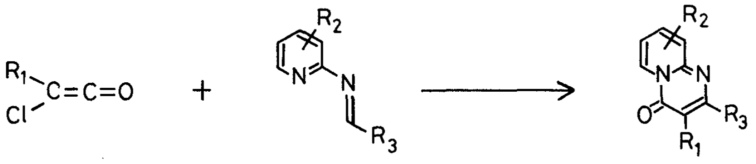
Reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**4**) with carboalkoxychloromethylenetriphenylphosphoranes (**5a**, **b**) gave an *E*, *Z* mixture of the corresponding alkyl 4,5,7-tri-*O*-benzyl-2-chloro-2,3-dideoxy-D-*ribo*-hept-2-enonates (**6a**, **b**). Cyclization of **6a**, **b** with triethylamine afforded exclusively the *β*-*C*-glycosides **7a**, **b** which were diastereomeric at the carbon bearing chlorine. Hydrolysis of **7a**, **b** with 5% aq. sodium hydroxide in dioxane gave the carboxylic acid **8**.Treatment of **8** with thionyl chloride (or trifluoroacetic anhydride) in the presence of triethylamine, followed by reaction with the 2-arylideneaminopyridine **2a** or ethyl *N*-(2-pyridyl)formimidates (**2b**, **c**) gave the corresponding fully protected pyrido[1,2-*a*]pyrimidine *C*-nucleosides (**15a**—**c**), which were deprotected with boron trichloride to give the *C*-nucleosides (**17b**, **c**).

Keywords——D-ribofuranose; phosphorane; Wittig reaction; *C*-nucleoside; [2+4]cycloaddition; chloroketene intermediate; pyrido[1,2-*a*]pyrimidine; *β*-*C*-ribofuranosyl glycoside; ^{13}C-NMR

Since formycin A bearing a fused pyrimidine ring, pyrazolo[4,3-*d*]pyrimidine, was found to have significant biological activities, many formycin A analogs having a [6+5]bicyclic heterocycle (fused six- and five-membered rings) have been synthesized.[2] However, little work has been done on the synthesis of *C*-nucleosides having a [6+6]bicyclic heterocycle.

Previously, we reported that haloketenes (**1**) underwent [2+4]cycloaddition with ethyl *N*-(2-pyridyl)formimidates (**2**, R_3=OEt)[3] or 2-arylideneaminopyridines (**2**, R_3=aryl)[4] to give the fused pyrimidinones **3**. In this paper, we describe the synthesis of pyrido[1,2-*a*]pyrimidine *C*-nucleosides *via* [2+4]cycloaddition of a chlororibofuranosylketene intermediate (**14**) derived from the *β*-*C*-glycoside which can be stereoselectively prepared by Wittig reaction of the protected D-ribose with chloromethylenetriphenylphosphorane.



1 **2** **3**

Chart 1

When 2,3,5-tri-*O*-benzyl-D-ribofuranose (**4**) was allowed to react with carbomethoxychloromethylenetriphenylphosphorane (**5a**) under reflux in acetonitrile, an *E*,*Z* mixture (*E*:*Z*=*ca.* 1:10) of methyl 4,5,7-tri-*O*-benzyl-2-chloro-2,3-dideoxy-D-*ribo*-hept-2-enonate (**6a**) was obtained in 71% yield. The ratio of *E* and *Z* products was determined by ^{1}H-NMR spectroscopy. Namely, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6a**, the signal due to the olefinic proton of the *E*-isomer is observed at δ 6.58 whereas that of the *Z*-isomer is observed at δ 7.16, at lower field, owing to the effect of an ester carbonyl group. The relative areas of these signals showed that the ratio of *E* and *Z* was 1 : 10. Similar reaction of **4** with the phosphorane **5b** gave a 76% yield of an *E*, *Z* mixture (1 : 10) of **6b**, which was chromatographically separable. Cyclization of **6a** and **6b** with triethylamine in acetonitrile gave the β-D-ribofuranosylglycosides **7a** (mp 76 °C) and **7b** (mp 56 °C) in 48 and 57% yields, respectively. In this reaction, the respective formations of the isomers **7'a** and **7'b** were observed, which were diastereomeric at the carbon bearing chlorine.

In order to determine the anomeric configuration of **7a, b**, we tried to transform **7a** into the isopropylidene derivatives **11** and **12**. Deprotection of **7a** with boron trichloride at −78 °C gave the *C*-glycosides **9** and **10**, which, without purification, were treated with 2,2-dimethoxypropane in the presence of 70% perchloric acid to give the isopropylidene drivatives **11** and **12**. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **11** shows the signals due to isopropylidene methyl carbons at δ 25.36 and δ 27.18, approximately in the range (25.5±0.2 and 27.5±0.2) expected for β-configuration.[6] Furthermore, similar treatment of a mixture of **7a** and **7'a** gave **11** (a diastereomeric mixture at the 2-position), whose ^{1}H- and ^{13}C-NMR spectra were consistent with those of the *C*-glycoside prepared by detritylation of methyl (2ξ)-3,6-anhydro-2-deoxy-2-chloro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*allo*-heptonate (**13**)[5] with *p*-toluenesulfonic acid in the presence of 2,2-dimethoxypropane. Therefore, **7a** (and **7'a**) was assigned as the β anomer.

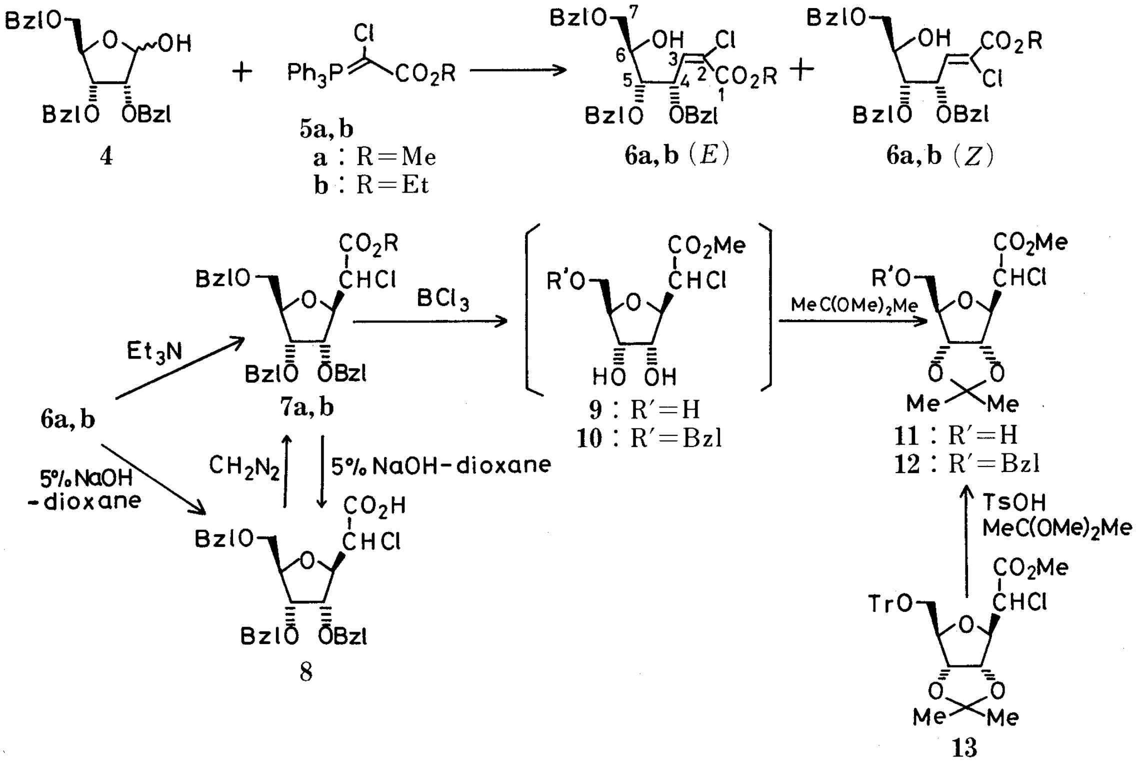


Chart 2

It has been reported that Wittig reaction of **4** with methoxycarbonylmethylenetriphenylphosphorane gives an *E*, *Z* mixture of linear compounds, and that the *E*-isomer, on treatment with base, cyclizes to an anomeric mixture of *C*-glycosides, whereas the same treatment of the *Z*-isomer gives exclusively a β-*C*-glycoside.[6] However, cyclization of both *E* and *Z*-isomers of **6a, b** with base gave only the β-*C*-glycosides **7a, b**, which are more versatile for the synthesis of *C*-nucleosides. The reason why only *β*-*C*-glycosides were obtained in our case is not clear.

Next, we investigated the conversion of **7a** into a ketene intermediate (**14**) with the intention of obtaining *C*-nucleosides. Compound **7a** was treated with 5% aqueous sodium hydroxide in dioxane to give a 45% yield of carboxylic acid **8** (mp 114—116 °C), which was also obtained by similar treatment of **6a**. In this reaction, the carboxylic acid **8′** diastereoisomeric to **8** at the carbon bearing chlorine was isolated by silica gel column chromatography.

Both **8** and **8′** were methylated with diazomethane to give **7a** and **7′a**, respectively. Thus, alkali treatment of **7a** did not cause epimerization and gave the *β*-*C*-glycoside **8** as a sole product.

Chlorination of **8** with thionyl chloride, followed by treatment with 2-furylideneaminopyridine (**2a**) in the presence of triethylamine, gave a protected pyrido[1,2-*a*]pyrimidine *C*-nucleoside **15a**, mp 94—95 °C, in 28% yield. The structure of **15a** was determined from the spectral data. Namely, the infrared (IR) spectrum shows absorption bands characteristic of pyrido[1,2-*a*]pyrimidine at 1670 and 1640 cm^{-1}.$^{7)}$ In the ^{1}H-NMR spectrum, the signals due to an anomeric proton (1′-H) and a proton at the *peri* position (6-H) were observed at δ 5.58 and 8.82, respectively.

Next, **8** was treated with trifluoroacetic anhydride in the presence of triethylamine to form a mixed anhydride, which reacted with ethyl *N*-(3-methyl-2-pyridyl)formimidate (**2b**) in the presence of triethylamine to give the *C*-nucleoside **15b** and the enamine **16** in 17 and 46% yields, respectively. The spectral data for **15b** are consistent with the pyrido[1,2-*a*]pyrimidine *C*-nucleoside structure. Based upon the following spectral data, the structure of **16** was determined to be 1-2′,3′,5′-tri-*O*-benzyl-*β*-D-ribofuranosyl-1-chloro-2-(3-methyl-2-pyridylamino)ethylene. The IR spectrum showed absorption bands due to NH and C=C of enamine at 3450 and 1670 cm^{-1}, respectively. In the ^{1}H-NMR spectrum, the signal due to an NH proton was observed at δ 6.50 as a doublet coupled with the olefinic proton (δ 7.95, d, $J=$ 12 Hz).

Similar treatment of **8** with trifluoroacetic anhydride, followed by reaction with ethyl *N*-(2-pyridyl)formimidate (**2c**) gave the pyrido[1,2-*a*]pyrimidine *C*-nucleoside **15c** in 10% yield. In this reaction, the enamine corresponding to **16** was not detected.

The mechanisms of formation of **15a—c** and **16** may be rationalized as follows. That is, electrophilic attack of the ketene intermediate **14**, derived from the acid chloride or mixed anhydride, gives rise to the zwitter ion A, cycloaddition of which forms the intermediate B. Elimination of hydrogen chloride from B gives the pyrido[1,2-*a*]pyrimidines **15a—c**, whereas hydrolysis of B affords the carboxylic acid C, which releases ethanol and carbon dioxide to produce the enamine **16**. Since the carboxylic acid corresponding to C was isolated from the reaction of dichloroketene with 2-benzylideneaminopyridine,$^{3b)}$ this mechanism seems to be reasonable. However, it is not clear why an enamine such as **16** was obtained only in the reaction of **2b** with **14**.

Deprotection of **15b** and **15c** with boron trichloride gave the pyrido[1,2-*a*]pyrimidine *C*-nucleosides **17b** and **17c** in 40 and 51% yields, respectively. In order to confirm the configuration of **17b, c** at the anomeric position, **17** was transformed into the 2′,3′-*O*-isopropylidene *C*-nucleoside **18** by treatment with 2,2-dimethoxypropane in the presence of 70% perchloric acid. The ^{13}C-NMR spectrum showed the signals due to two methyl carbons of the isopropylidene group at δ 25.71 and 27.83, indicating *β* configuration.

In conclusion, we were able to obtain selectively the *β*-*C*-glycoside from the reaction of protected D-ribose and the *α*-chloromethylenetriphenylphosphorane, and we found that the *C*-glycoside could serve as a reagent for the synthesis of *C*-nucleoside. This is the first report of the synthesis of a *C*-nucleoside having a [6+6]bicyclic heterocycle *via* the ketene intermediate.

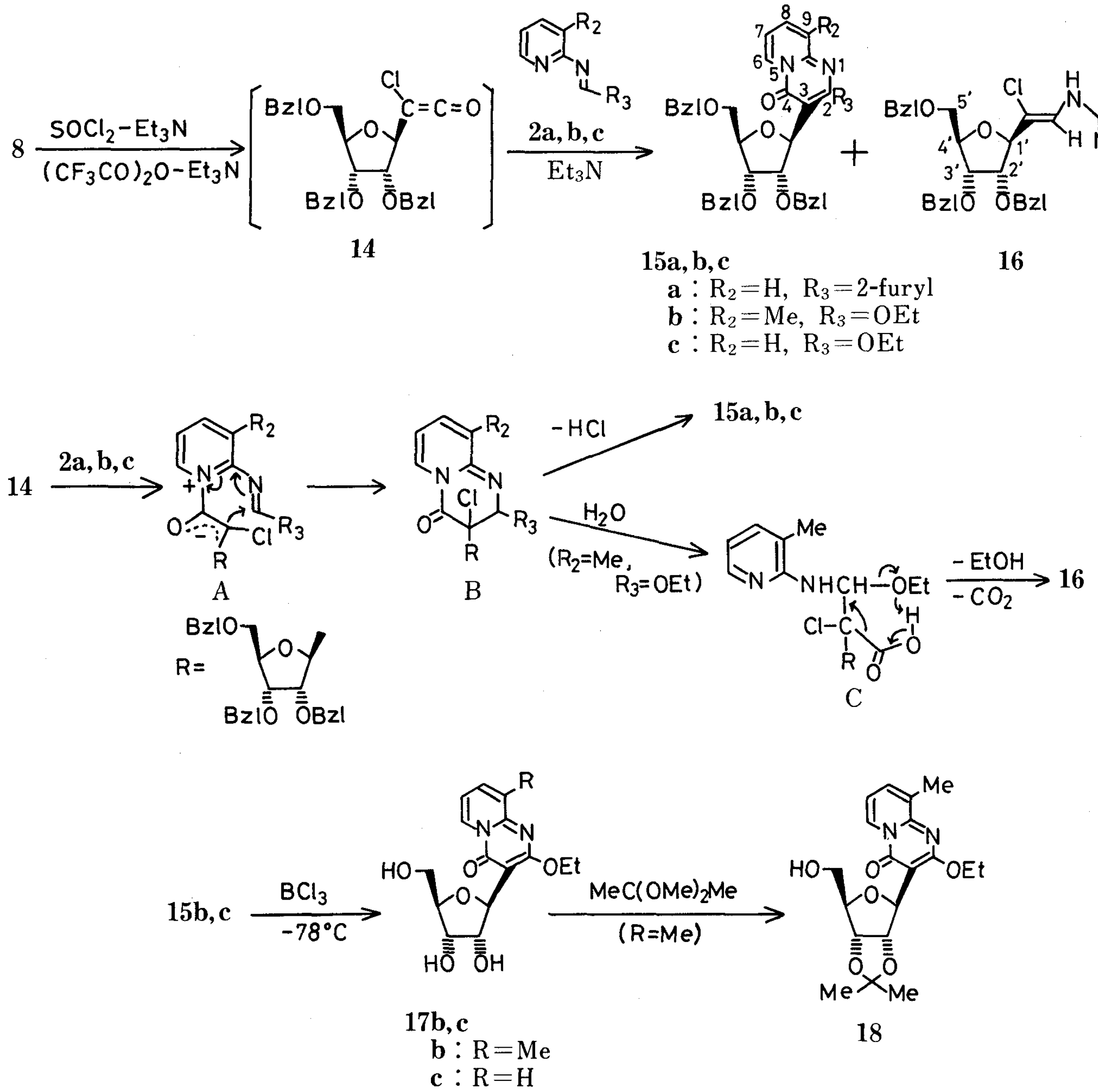


Chart 3

Experimental

IR spectra were measured with a JASCO A-102 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM FX-100 spectrometer with tetramethylsilane as an internal standard. The optical rotations were measured with a JASCO DIP-4B spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi model 124 spectrophotometer. Wako gel (C-200) was employed for silica gel column chromatography. All samples for elemental analyses were obtained by purification through silica gel column chromatography or recrystallization, followed by vacuum (5 mmHg) drying at 40 °C for 24 h.

Methyl *E*- and *Z*-4,5,7-Tri-*O*-benzyl-2-chloro-2,3-dideoxy-D-*ribo*-hept-2-enonate (6a)——A mixture of **4**[8] (1.85 g, 4.4 mmol) and **5a**[9] (1.95 g, 5.3 mmol) in acetonitrile (20 ml) was heated under reflux for 8 h. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (100 g) column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave the product **6a** (E : Z = 1 : 10), colorless oil, 1.59 g (71%). *Anal.* Calcd for $C_{29}H_{31}ClO_6$: C, 68.16; H, 6.11; Cl, 6.94. Found: C, 68.40; H, 6.25; Cl, 6.92. IR ($CHCl_3$): 3750, 1725, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (1H, br, OH), 3.45—3.61 (2H, m, 7-H), 3.76 (1H × 10/11, s, OMe, *Z* form), 3.81 (1H × 1/11, s, OMe, *E* form), 4.82 (1H × 10/11, dd, $J_{3,4}$ = 8 Hz, $J_{4,5}$ = 3 Hz, 4-H, *Z* form), 5.08—5.22 (1H × 1/11, m, 4-H, *E* form), 6.58 (1H × 1/11, d, $J_{3,4}$ = 10 Hz, 3-H, *E* form), 7.16 (1H × 10/11, d, $J_{3,4}$ = 8 Hz, 3-H, *Z* form), 7.20—7.32 (15H, m, Ar-H).

Methyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-chloro-2-deoxy-D-*allo*-heptonate (7a) and Its Isomer (7′a)——1) A solution of **6a** (0.98 g, 1.9 mmol) and triethylamine (0.96 g, 9.6 mmol) in acetonitrile (10 ml) was allowed to stand at 15 °C for 3 h. The mixture was concentrated *in vacuo*, and the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave the product **7a**, colorless needles (from ether–hexane), mp 76 °C, $[\alpha]_D^{20}$ +35.7 ° (c=2.8, $CHCl_3$) 0.47 g (48%). High-resolution MS Calcd for $C_{22}H_{24}ClO_6$: 419.1260. Found: 419.1264 ($M^+ - PhCH_2$) IR ($CHCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49—3.56 (2H, m, 7-H), 3.71 (3H, s, OMe), 7.23—7.32 (15H, m, Ar-H). Further elution with the same solvent gave an oily substance (0.1 g) which contained **7a** and its diastereoisomer **7′a** (*ca.* 1 : 2) (*vide infra*) at the 2-carbon bearing chlorine.

2) A solution of **8** (0.1 g) in ether (2 ml) was added to excess diazomethane–ether solution at room temperature. The solvent was evaporated off, and the crystalline residue was recrystallized from ether–hexane to give **7a** (0.1 g, 98%).

3) Following the same procedure as described above, the diastereoisomer **8′** was methylated with diazomethane in ether to give compound **7′a** as an oily substance (quantitative yield, $[\alpha]_D^{20}$ +15.2 ° (c=3.7, $CHCl_3$). IR ($CHCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (2H, d, $J_{6,7}$=5 Hz, 7-H), 3.67 (3H, s, OMe), 7.20—7.32 (15H, m, Ar-H).

Ethyl *E*- and *Z*-4,5,7-Tri-*O*-benzyl-2-chloro-2,3-dideoxy-D-*ribo*-hept-2-enonate (6b)——A mixture of **4** and **5b** in acetonitrile (40 ml) was heated under reflux for 12 h. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (9 : 1) gave the product **6b** (E : Z = 1 : 10), foam, 10 g (76%). Compound **6b** was rechromatographed on a silica gel column using the same solvent as the eluent to give **6b** (E) and **6b** (Z), each as a colorless oil. **6b** (E): *Anal.* Calcd for $C_{30}H_{33}ClO_6$: C, 68.63; H, 6.34. Found: C, 68.43; H, 6.37. IR ($CHCl_3$): 3570, 1725, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.45—3.61 (2H, m, 7-H), 5.15 (1H, d, $J_{3,4}$=10 Hz, 4-H), 6.55 (1H, d, $J_{3,4}$=10 Hz, 3-H), 7.20—7.28 (15H, m, Ar-H). **6b** (Z): *Anal.* Calcd for $C_{30}H_{33}ClO_6$: C, 68.63; H, 6.34. Found: C, 68.13; H, 6.39. IR ($CHCl_3$): 3570, 1725, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 3.45—3.61 (2H, m, 7-H), 4.83 (1H, dd, $J_{3,4}$=9 Hz, $J_{4,5}$=3 Hz, 4-H), 7.15 (1H, d, $J_{3,4}$=9 Hz, 3-H).

Ethyl 3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-chloro-2-deoxy-D-*allo*-heptonate (7b)——A solution of **6b** (0.3 g) and triethylamine (50 mg) in acetonitrile (5 ml) was allowed to stand at room temperature overnight. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (8 : 1) gave the product **7b**, colorless needles (hexane–ether), mp 56 °C, 170 mg (56%). *Anal.* Calcd for $C_{30}H_{33}ClO_6 \cdot H_2O$: C, 66.35; H, 6.50. Found: C, 66.42; H, 5.98. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 3.60 (2H, d, $J_{6,7}$=5 Hz, 7-H), 7.28—7.36 (15H, m, Ar-H).

3,6-Anhydro-4,5,7-tri-*O*-benzyl-2-chloro-2-deoxy-D-*allo*-heptonic Acid (8)——1) A solution of **7a** (4.6 g, 9 mmol) in 5% aqueous sodium hydroxide (54 ml) and dioxane (54 ml) was stirred for 18 h at room temperature. The mixture was neutralized with dil. hydrochloric acid, and concentrated *in vacuo* to half the initial volume. The residue was extracted with ether. The extract was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a crystalline substance (4.5 g). Recrystallization from ether–hexane gave the product **8**, mp 114—116 °C, $[\alpha]_D^{20}$ +36.8 ° (c=9, MeOH) colorless needles, 2.03 g (45%). **8**: *Anal.* Calcd for $C_{28}H_{29}ClO_6$: C, 67.67; H, 5.88. Found: C, 67.45; H, 5.70. IR ($CHCl_3$): 1760, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (1H, dd, $J_{7a,7b}$=10 Hz, $J_{6,7}$=3 Hz, 7a-H), 3.65 (1H, dd, $J_{7a,7b}$=10 Hz, $J_{6,7}$=3 Hz, 7b-H), 5.44 (1H, br, OH), 7.23—7.31 (15H, m, Ar-H). The mother liquor was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave the product **8** and its diastereoisomer **8′**, colorless oil. **8′**: *Anal.* Calcd for $C_{28}H_{29}ClO_6 \cdot 2/3H_2O$: C, 66.07; H, 6.01. Found: C, 65.77; H, 5.90. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, d, $J_{6,7}$=6 Hz, 7-H), 7.20—7.34 (15H, m, Ar-H), 8.35 (1H, br, CO_2H).

2) Following the same procedure as described above, compound **7b** was treated with 5% aqueous sodium hydroxide in dioxane to give the product **8** (62%). The isomer **8′** (more polar than **8**) was detected by thin layer chromatography (TLC) of the mother liquor.

Methyl 3,6-Anhydro-2-chloro-2-deoxy-4,5-*O*-isopropyridene-D-*allo*-heptonate (11) and Methyl 3,6-Anhydro-7-*O*-benzyl-2-chloro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonate (12)——1) A solution of **7a** (0.68 g, 1.3 mmol) in anhydrous dichloromethane (8 ml) was added dropwise to a solution of boron trichloride (24 mmol) in anhydrous dichloromethane (19 ml) at −78 °C with stirring. This mixture was stirred at −78 °C for 5 h, then a mixture of abs. methanol (20 ml) and anhydrous dichloromethane (20 ml) was added dropwise at −78 °C with stirring. The reaction temperature was raised gradually to room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was coevaporated with abs. methanol *in vacuo* six times. The resulting residue was dissolved in a solution of 70% perchloric acid (0.05 ml) and 2,2-dimethoxypropane (0.6 ml) in acetone (10 ml). The reaction mixture was stirred for 2 h at room temperature, then neutralized with conc. aqueous NH_4OH, and concentrated *in vacuo*. The residue was dissolved in chloroform. The solution was washed with water twice, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (15 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1—3 : 1) gave the products **11** (90 mg, 25%) and **12** (190 mg, 39%). **11** (colorless oil): *Anal.* Calcd for $C_{11}H_{17}ClO_6$: C, 47.07; H, 6.10; Cl, 12.63. Found: C, 46.81; H, 6.19; Cl, 12.53. IR ($CDCl_3$): 3550, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, isopropylidene-Me), 1.55 (3H, s, isopropylidene-Me), 2.50 (1H, s, OH), 3.67—3.77 (2H, m, 7-H), 3.84 (3H, s, OMe). ^{13}C-NMR ($CDCl_3$) δ: 25.36, 27.18 (isopropylidene-Me), 53.25 (ester-OMe), 56.42 (2-C), 62.82 (7-C), 81.49, 83.02, 85.30, 86.07 (3-C, 4-C, 5-C, 6-C), 113.95 (isopropylidene-C), 168.15 (ester-CO). **12** (colorless oil): *Anal.* Calcd for $C_{18}H_{23}ClO_6$: C, 58.30; H, 6.25; Cl, 9.56. Found: C, 57.87; H, 6.33; Cl, 9.60. IR ($CDCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, isopropylidene-Me), 1.55 (3H, s, isopropylidene-Me), 3.51—

3.61 (2H, m, 7-H), 3.82 (3H, s, OMe), 7.32 (5H, s, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 25.36, 27.18 (isopropylidene-Me), 52.96 (ester-OMe), 55.48 (2-C), 71.10 (7-C), 73.74 (benzyl-CH_2), 82.72, 83.66, 84.95, 86.54 (3-C, 4-C, 5-C, 6-C), 113.37 (isopropylidene-C), 127.87, 128.46 (benzyl-CH), 137.38 (benzyl-C), 168.44 (ester-CO).

2) In a manner similar to that described above in 1), a mixture of **7a** ann **7a′** (0.5 g, 0.95 mmol) was treated with boron trichloride (47.5 mmol), followed by 2,2-dimethoxypropane to give the product **11** (173 mg, 65%), which was identical with that obtained from **13** (*vide infra*).

3) A solution of **13** (100 mg, 0.2 mmol), 2,2-dimethoxypropane (4 ml), and *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) in acetone (6 ml) was stirred at room temperature for 5 h. Sodium bicarbonate (0.6 g, 7.1 mmol) was added, and the resulting mixture was stirred for 2 h. The precipitates were filtered off, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (15 g) column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave the product **11**, pale yellow oil, 20 mg (36%). High-resolution MS Calcd for $C_{10}H_{14}ClO_6$: 265.0478. Found: 265.0466 ($M^+ - CH_3$). IR ($CDCl_3$): 3580, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, isopropylidene-Me), 1.55 (3H, s, isopropylidene-Me), 3.65—3.70 (2H, m, 7-H), 3.84 (3H, s, -OMe). ^{13}C-NMR ($CDCl_3$) δ: 25.36, 25.48, 27.24, 27.42 (isopropylidene-Me), 53.31 (ester-OMe), 56.54, 57.54 (2-C), 62.64, 62.88 (7-C), 80.96, 81.43, 81.96, 83.02, 84.19, 85.25, 86.07 (3-C, 4-C, 5-C, 6-C), 114.02, 114.49 (isopropylidene-C).

3-2′,3′,5′-Tri-*O*-benzyl-*β*-D-ribofuranosyl-2-(2-furyl)pyrido[1,2-*a*]pyrimidin-4-one (15a)——A solution of **8** (0.6 g, 1.2 mmol) and thionyl chloride (3 ml) in anhydrous ether (3 ml) was refluxed for 2 h. The mixture was concentrated *in vacuo*, and the residue was coevaporated *in vacuo* with dry benzene. The resulting residue was dissolved in anhydrous 1,2-dimethoxypropane (DME) (5 ml). The solution was added dropwise to a solution of **2a**$^{4)}$ (0.4 g, 2.4 mmol) and triethylamine (0.36 g, 3.6 mmol) in anhydrous DME (5 ml) below 5 °C with stirring. After being stirred for 4 h, the mixture was allowed to stand at room temperature overnight. The precipitates ($Et_3N \cdot HCl$) were filtered off, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave a mixture of 2-aminopyridine and **15a**, which was dissolved in chloroform. The solution was washed with 10% hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the product **15a**, colorless prisms (from hexane–ether), mp 94—95 °C, 210 mg (28%). *Anal.* Calcd for $C_{38}H_{34}N_2O_6 \cdot CH_3CO_2CH_2CH_3$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.56; H, 5.71; N, 4.07. IR ($CDCl_3$): 1720 (ethyl acetate), 1675, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68—3.88 (2H, m, 5′-H), 5.58 (1H, d, $J_{1',2'}=$ 5 Hz, 1′-H), 6.51 (1H, dd, $J=4$ Hz, $J=2$ Hz, 2-furyl-H), 8.82 (1H, m, 6-H).

3-2′,3′,5′-Tri-*O*-benzyl-*β*-D-ribofuranosyl-2-ethoxy-9-methylpyrido[1,2-*a*]pyrimidin-4-one (15b) and 1-2′,3′,5′-Tri-*O*-benzyl-*β*-D-ribofuranosyl-1-chloro-2-(3-methyl-2-pyridylamino)ethylene (16)——A solution of triethylamine (242 mg, 2.4 mmol) and trifluoroacetic anhydride (0.5 g, 2.4 mmol) in anhydrous dichloromethane (1 ml) was added dropwise to a solution of **8** (0.99 g, 2 mmol) in anhydrous dichloromethane (4 ml) at -5—-10 °C with stirring. The mixture was stirred at this temperature for 30 min. The solution was added dropwise to a solution of **2b**$^{10)}$ (0.49 g, 3 mmol) and triethylamine (0.6 g, 6 mmol) in anhydrous dichloromethane (5 ml) at -5—-10 °C with stirring. The reaction temperature was raised gradually to room temperature. After being stirred for 8 h, the mixture was allowed to stand for 48 h. The reaction mixture was poured into ice-water, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue (1.9 g) was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (9 : 1) gave the product **16**, colorless needles (from hexane–ether), mp 66 °C, $[\alpha]_{\mathrm{D}}^{20}$ $+5.8°$ ($c=2.4$, MeOH) 0.57 g (46%). Further elution with hexane–ethyl acetate (2 : 1) gave the product **15b**, foam, $[\alpha]_{\mathrm{D}}^{20}$ $-11.1°$ ($c=4.8$, MeOH) 0.2 g (17%). **15b**: High-resolution MS Calcd for $C_{37}H_{38}N_2O_6$: 606.2728. Found: 606.2696. IR ($CHCl_3$): 1670, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, $J=7$ Hz, $-OCH_2C\underline{H}_3$), 2.48 (3H, s, 9-Me), 3.72 (2H, m, 5′-H), 5.53 (1H, d, $J_{1',2'}=5$ Hz, 1′-H), 6.93 (1H, t, $J=7$ Hz, 7-H), 7.08—7.32 (15H, m, Ar-H), 7.53 (1H, d, $J_{7,8}=7$ Hz, 8-H), 8.83 (1H, d, $J_{6,7}=7$ Hz, 6-H). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 225, 267, 331, 338. **16**: *Anal.* Calcd for $C_{34}H_{35}ClN_2O_4$: C, 71.50; H, 6.18; Cl, 6.21; N, 4.91. Found: C, 71.30; H, 6.21; Cl, 6.16; N, 4.71. IR ($CHCl_3$): 3450, 1670, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, pyridyl 3-Me), 3.57 (2H, d, $J_{4',5'}=5$ Hz, 5′-H), 4.73 (1H, d, $J_{1',2'}=6$ Hz, 1′-H), 6.50 (1H, d, $J_{7,8}=12$ Hz, NH), 6.67 (1H, dd, $J_{2,3}=5$ Hz, $J_{3,4}=7$ Hz, pyridyl 3-H), 7.95 (1H, d, $J_{7,8}=12$ Hz, olefinic proton), 8.02 (1H, m, pyridyl 2-H).

3-2′,3′,5′-Tri-*O*-benzyl-*β*-D-ribofuranosyl-2-ethoxypyrido[1,2-*a*]pyrimidin-4-one (15c)——A solution of triethylamine (0.83 g, 8.2 mmol) and trifluoroacetic anhydride (1.72 g, 8.2 mmol) in anhydrous dichloromethane (6 ml) was added dropwise to a solution of **8** (3.4 g, 6.8 mmol) in anhydrous dichloromethane (6 ml) at -5—-10 °C with stirring. The mixture was stirred at room temperature for 3 h. The solution was added dropwise to a solution of **2c**$^{10)}$ (2.06 g, 13.6 mmol) and triethylamine (2.06 g, 20.4 mmol) in anhydrous dichloromethane (24 ml) at -5—-10 °C with stirring. The reaction temperature was raised gradually to room temperature. After being stirred for 8 h, the mixture was allowed to stand for 12 h. The reaction mixture was poured into ice-water, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (80 g) column chromatography. Elution with hexane–ethyl acetate (2 : 1) gave the product **15c**, foam, $[\alpha]_{\mathrm{D}}^{20}$ $-2.3°$ ($c=5.3$, MeOH) 0.4 g (10%). *Anal.* Calcd for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 73.48; H, 6.20; N, 4.47. IR ($CDCl_3$): 1675, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz, $-OCH_2C\underline{H}_3$), 3.67—3.76 (2H, m, 5′-H), 5.50 (1H, d, $J_{1',2'}=4$ Hz), 7.60—7.78 (1H, m, 8-H), 8.94 (1H, d, $J_{6,7}=7$ Hz, 6-H).

2-Ethoxy-3-(*β*-D-ribofuranosyl)-9-methylpyrido[1,2-*a*]pyrimidin-4-one (17b)——A solution of **15b** (0.47 g, 0.77 mmol) in dichloromethane (5 ml) was added dropwise to boron trichloride chlorobenzene solution (4.26 mmol/1 ml) (7 ml, 29.82 mmol) in dichloromethane (12 ml) at −78 °C with stirring. This was stirred at −78 °C for 1.5 h, then a mixture of methanol (10 ml) and dichloromethane (10 ml) was added dropwise with stirring. The reaction temperature was raised gradually to room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was coevaporated with methanol six times. The resulting residue was subjected to silica gel (20 g) column chromatography. Elution with ethyl acetate–acetone–methanol–water (50 : 1 : 1 : 1) gave the product **17b**, foam, 0.11 g (40%). *Anal.* Calcd for $C_{16}H_{20}N_2O_6 \cdot H_2O$: C, 54.23; H, 6.26; N, 7.91. Found: C, 54.38; H, 5.89; N, 7.86. IR (KBr): 3400, 1655, 1625 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.43 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.49 (3H, s, 9-Me), 3.59—3.84 (2H, m, 5′-H), 4.85 (2H, s, H_2O), 5.02 (1H, d, $J_{1',2'}$=10 Hz, 1′-H), 7.11 (1H, t, J=7 Hz, 7-H), 7.72 (1H, d, $J_{7,8}$=7 Hz, 8-H), 8.81 (1H, d, $J_{6,7}$=7 Hz, 6-H). UV $\lambda_{\max}^{\mathrm{MeOH}}$ nm: 224, 267, 331, 338.

2-Ethoxy-3-(β-D-ribofuranosyl)pyrido[1,2-*a*]pyrimidin-4-one (17c)——A solution of **15c** (0.4 g, 0.67 mmol) in anhydrous dichloromethane (30 ml) was added dropwise to a solution of boron trichloride (20 mmol) in anhydrous dichloromethane (20 ml) at −78 °C with stirring. This was stirred at −78 °C for 5 h, then a mixture of absolute methanol (15 ml) and anhydrous dichloromethane (15 ml) was added dropwise with stirring. The reaction temperature was raised gradually to room temperarure. The reaction mixture was concentrated *in vacuo*, and the residue was coevaporated with absolute methanol six times. The resulting residue was subjected to silica gel (20 g) column chromatography. Elution with ethyl acetate–acetone–methanol–water (50 : 1 : 1 : 1) gave the product **17c**, foam, $[\alpha]_D^{20}$ −45.5° (c=0.6, MeOH) 0.11 g (51%). High-resolution MS Calcd for $C_{15}H_{18}N_2O_6$: 322.1164. Found: 322.1143. IR (KBr): 3400, 1665, 1630 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.41 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 5.02 (1H, d, $J_{1',2'}$=10 Hz, 1′-H), 7.15—7.29 (1H, m, 7-H), 7.51 (1H, d, $J_{8,9}$=9Hz, 8-H), 7.77—7.96 (1H, m, 8-H), 8.96 (1H, d, $J_{6,7}$=7 Hz, 6-H).

2-Ethoxy-3-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl-9-methylpyrido[1,2-*a*]pyrimidin-4-one (18)——A solution of **17** (80 mg, 0.24 mmol), 2,2-dimethoxypropane (0.5 ml) and a catalytic amount of 70% perchloric acid in acetone (3 ml) was stirred for 2 h. The mixture was neutralized with conc. aqueous ammonium hydroxide, and concentrated *in vacuo*. The residue was subjected to silica gel (10 g) column chromatography. Elution with hexane–ethyl acetate gave the product **18**, colorless prisms (from hexane–ethyl acetate), mp 154 °C, 40 mg (44.7%). *Anal.* Calcd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.44; H, 6.48; N, 7.32. IR (KBr): 3420, 1660, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, isopropylidene-Me), 1.43 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 1.63 (3H, s, isopropylidene-Me), 2.51 (3H, s, 9-Me), 3.73 (1H, dd, $J_{5',5'}$=12 Hz, $J_{4',5'}$=2 Hz, 5′-H), 3.92 (1H, dd, $J_{5',5'}$=12 Hz, $J_{4',5'}$=3 Hz, 5′-H), 5.45 (1H, d, $J_{1',2'}$=6 Hz, 1′-H), 7.01 (1H, t, J=7 Hz, 7-H), 7.60 (1H, d, $J_{7,8}$=7 Hz, 8-H), 8.90 (1H, d, $J_{6,7}$=7Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 14.50 (ester-Me), 17.67 (9-Me), 25.71, 27.83 (isopropylidene-Me), 63.06, 63.58 (5′-C, ester-CH_2), 79.02, 82.78, 84.36 (1′-C, 2′-C, 3′-C, 4′-C), 113.25 (isopropylidene-C), 114.42 (7-C), 125.70 (8-C), 136.21 (6-C).

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