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# Synthesis of novel nucleosides and stereoselectivity of N-glycosidation

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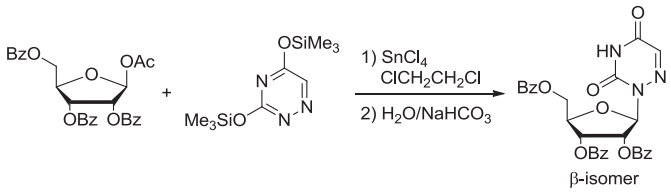
ABSTRACT

An efficient synthetic route for novel nucleosides has been realized. We report the formation of α-isomers in spite of neighboring group participation by the benzoyl group at the 2-position in N-glycosidation as well as discuss the stereoselectivity observed. We also found that non-silylated pyrimidin-2(1*H*)-ones and pyrimidin-2(1*H*)-thiones having aromatic structures reacted with 1-fluororibose in the presence of a Lewis acid to give the corresponding nucleosides in good to high yield.



## 1. Introduction

Natural occurring or artificial nucleosides are fundamental bioactive compounds.[1] Their biological activities include antitumor, anticancer, antibacterial, antiviral etc. Some nucleosides have been reported and used in the medical and pharmaceutical fields.[2,3] Consequently, development of their synthetic method and application in the medical field is in high demand. So far, many synthetic methods of nucleosides[4,5] and the methods not requiring heavy metals have been proposed.[6] The Vorbrüggen reaction, a representative example of glycosidation reaction, uses a silyl group to increase nucleophilicity (Scheme 1).[6c,7]



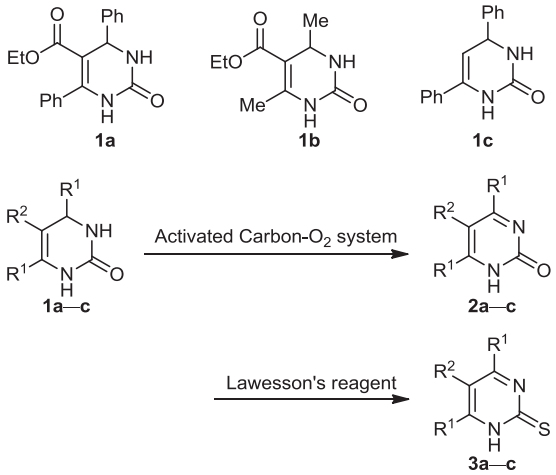

**Scheme 1.** Vorbrüggen reaction.

The neighboring group participation by a carbonyl group, such as the acetyl and benzoyl moieties at the 2-position is known to control the stereochemistry of the Vorbrüggen reaction with ribofuranoside, giving the β-isomer. Herein, we will report an efficient route for novel nucleosides and discuss the stereoselectivity observed in N-glycosidation.

## 2. Results and discussion

Dihydropyrimidin-2(1*H*)-ones (**1a**–**c**) were prepared according to previously reported method,[8] followed by treatment with activated carbon in $O_2$ atmosphere to afford pyrimidin-2(1*H*)-ones (**2a**–**c**)[9] (Scheme 2).

Further reactions with Lawesson's reagent gave pyrimidin-2(1*H*)-thiones (**3a**–**c**) in good to moderate yield. The detailed




**Scheme 2.** Synthesis of pyrimidin-2(1*H*)-ones and corresponding thiones.

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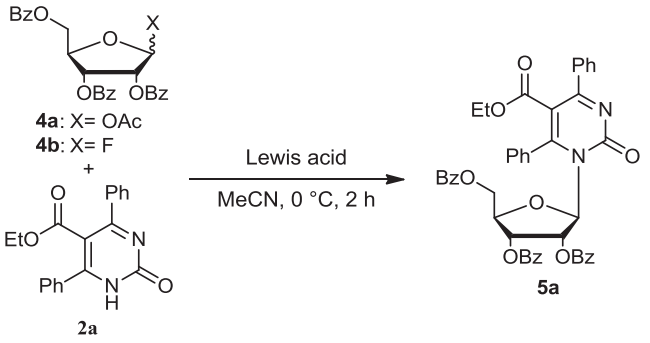
synthetic method of pyrimidin-2(1*H*)-ones and pyrimidin-2(1*H*)-thiones is given in the supplementary data. We first examined the nature of the Lewis acids ($Me_3SiOTf$, $SnCl_4$, and $BF_3\cdot OEt_2$) and leaving groups (Table 1). 2,3,5-Tri-*O*-benzoyl-D-*ribo*-furanosyl

**Table 1**
Optimization of the leaving group and Lewis acid




| Entry[a] | X | Lewis acid | Yield/%[b] | Isomer[c] |
|---|---|---|---|---|
| 1 | | $Me_3SiOTf$ | 11 (57) | β |
| 2 | β-OAc | $SnCl_4$ | 49 (15) | β |
| 3 | | $BF_3\cdot OEt_2$ | 31 (50) | β |
| 4 | | $Me_3SiOTf$ | 31 (24) | β |
| 5 | F (α:β=50:50) | $SnCl_4$ | 73 (0) | β |
| 6 | | $BF_3\cdot OEt_2$ | 53 (0) | β |

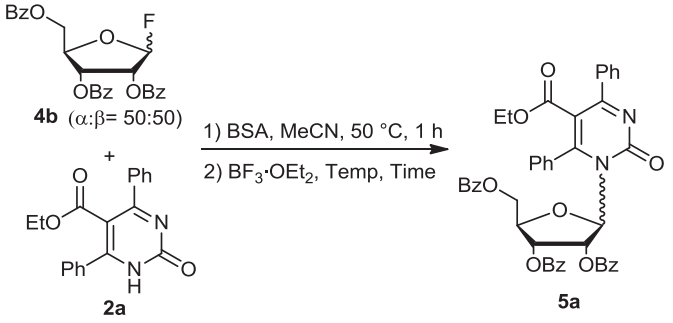
[a] The Lewis acid (3.7 equiv) was added to a mixture of substrate (**4a** or **4b**) and **2a** (1.3 equiv) in MeCN was added and stirred for 2 h at 0 °C.
[b] Isolated yield after silica gel column chromatography. The values in the parentheses indicate the yield of the recovered starting material.
[c] α-Isomer was not obtained.

fluoride[10] (**4b**) was prepared by fluorination of commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**4a**). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose as the substrate gave the products in low to moderate yield (11–49%) (entries 1–3 in Table 1). On the other hand, fluoro saccharides disappeared completely (entries 5 and 6) and the corresponding nucleosides were obtained in moderate yield as the β-isomers. Defluorination seemed to proceed well using $SnCl_4$ or $BF_3\cdot OEt_2$ as the Lewis acid. In all reactions, the α-isomer was not isolated. For easier manipulation, $BF_3\cdot OEt_2$ was selected to further optimize the reaction. Reducing the amount of $BF_3\cdot OEt_2$ to less than 3.7 equiv resulted in low yield. It should be noted that coordination of $BF_3\cdot OEt_2$ to pyimidin-2(1*H*)-one was detected by $^1H$ NMR, suggesting trapping of the Lewis acid by pyrimidin-2(1*H*)-one. The amount of Lewis acid as the active catalyst is reduced by the coordination. The trap might reduce both the nucleophilicity and the reactivity of pyrimidin-2(1*H*)-ones. However, the reducing nucleophilicity has smaller effect on the yield of the product than reducing amount of active Lewis acid because excess amount of $BF_3\cdot OEt_2$ (3.7 equiv) increased the yield of the product.

It should be mentioned that the glycosidation reaction did not proceed when non-aromatic ethyl 3,4-dihydro-4,6-diphenylpyrimidin-2(1*H*)-one-carboxylate (**1a**) was used as the nucleophile. This indicates that a lone pair in the σ orbital on a nitrogen in aromatic pyrimidin-2(1*H*)-ones (**2a**–**c**) is essential to promote nucleophilic attack.

Next, we examined the glycosidation condition using *N*,*O*-bistrimethysilylacetamide (BSA)[11] as the silylation reagent to promote the reaction (Table 2). Silylation reagent was added to the corresponding substrate and pyrimidinone in MeCN and stirred at 50 °C for 1 h. After silylation had completed, the reaction mixture was cooled to 0 °C, followed by slow addition of $BF_3\cdot OEt_2$. After stirring under the indicated conditions, the reaction was quenched with aqueous $NaHCO_3$ at 0 °C, followed by work-up and purification.

**Table 2**
Effect of temperature on the α:β isomer ratio




| Entry[a] | Temp/°C | Time/h | Yield/%[b] | α:β[c] |
|---|---|---|---|---|
| 1 | −30 | 3 | 51 | 3:97 |
| 2 | −30 | 24 | 58 | 0:100 |
| 3 | 0 | 1 | 93 | 16:84 |
| 4 | 0 | 24 | 88 | 0:100 |
| 5 | 24 | 1 | 94 | 15:85 |
| 6 | 26 | 12 | 60 | <2:98[d] |
| 7 | 50 | 1 | 85 | 24:76 |
| 8 | 50 | 6 | 39 | <5:95[d] |

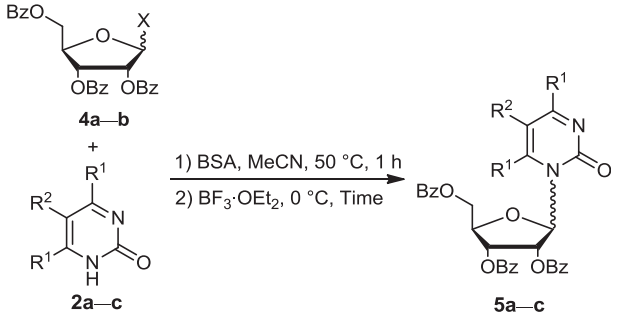
[a] BSA (1.9 equiv) was added to a mixture of **4b** and **2a** (1.3 equiv) in MeCN and stirred for 1 h at 50 °C, followed by the addition of $BF_3\cdot OEt_2$ (3.7 equiv) at 0 °C and stirred under indicated conditions.
[b] Isolated yield after silica gel column chromatography.
[c] α:β ratio was determined after isolation of each isomer.
[d] α:β ratio was determined by $^1H$ NMR analysis.

Products were obtained in moderate to excellent yield (51–94%). Interestingly, α-isomer was isolated despite the benzoyl moiety at the 2-position, which was expected to function as the neighboring participation group (entries 1, 3, 5, and 7). Formation and isolation of the minor α-isomer in the presence of acyl group at 2-position is rare.[12]

The reaction at a low temperature (−30 °C) resulted in moderate yield, however, it was controlled well by the kinetic effect (entry 1). Stirring for 24 h at −30 °C gave high β-selectivity (α:β=0:100) of the product (entry 2). We also examined the reaction at 0 °C, room temperature (24 °C), and 50 °C (entries 3, 5, and 7, respectively). In particular, glycosidation at 50 °C gave the highest α-ratio (α:β=24:76) (entry 7). We examined the effect of the reaction time at each temperature and found that the α-ratio decreased (entries 4, 6, and 8). Although the α-ratio increased with the increasing temperature, long time stirring gave the product with high β-selectivity compared with short reaction time (1–3 h). Stirring at 70 °C for 30 min gave the product in 60% yield (α:β=31:69). We also examined the amount of Lewis acid under fixed conditions (0 °C, 1 h) and found that the α-ratio decreased as the amount of Lewis acid ($BF_3\cdot OEt_2$) was increased to 3.7 and 10.0 equiv (α:β=16:84 (93%), α:β=0:100 (84%), respectively). An attempt to reduce the amount of Lewis acid to 1.8 equiv failed, resulting in 60% yield (α:β=19:81). These results suggested that conversion of the α-isomer into the β-isomer was promoted by the Lewis acid. Accordingly, we exposed the isolated α-isomer to $BF_3\cdot OEt_2$ in the presence of silylpyrimidinone in $CD_3CN$ at 50 °C and observed gradual formation of the β-isomer by $^1H$ NMR. Thus, we assume that the anomerization of the nucleoside proceeded via the oxocarbenium ion catalyzed by the Lewis acid.[13] Conversion of each isomer via the $S_N2$ mechanism would be unlikely because of the bulky structures of pyrimidin-2(1*H*)-ones and nucleosides. Other pyrimidin-2(1*H*)-ones (**2b**–**c**) were introduced (Table 3) for comparison of nucleophile size.

The α:β ratio of product **5b** was 30:70 using ethyl 4,6-dimethyl pyrimidin-2(1*H*)-one-5-carboxylate (**2b**) as the nucleophile (entry 2), and introducing 4,6-diphenylpyrimidin-2(1*H*)-one (**2c**) afforded

**Table 3**
Synthesis of glycosides with various pyrimidin-2(1*H*)-ones




| Entry[a] | X | Time/h | $R^1$ | $R^2$ | Product | Yield/%[b] | α:β[c] |
|---|---|---|---|---|---|---|---|
| 1 | | | Ph | $CO_2Et$ | **5a** | 84 (0) | 12:88 |
| 2 | F (α:β=50:50) | 2 | Me | $CO_2Et$ | **5b** | 90 (0) | 30:70 |
| 3 | | | Ph | H | **5c** | 93 (0) | 10:90 |
| 4 | | | Ph | $CO_2Et$ | **5a** | 62 (26) | 0:100 |
| 5 | β-OAc | 3 | Me | $CO_2Et$ | **5b** | 34 (16) | 0:100 |
| 6 | | | Ph | H | **5c** | 46 (52) | 0:100 |

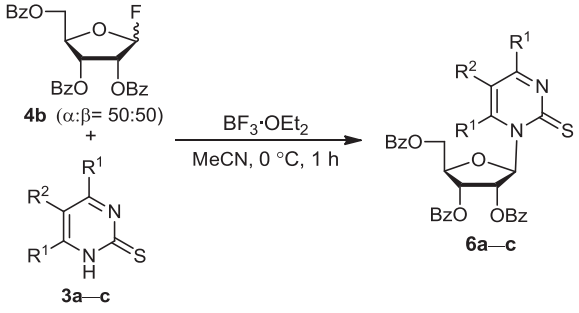
[a] To a mixture of substrate (**4a** or **4b**) and **2a**–**c** (1.2 equiv) in MeCN was added BSA (2.0 equiv) and stirred for 1 h at 50 °C, followed addition of $BF_3·OEt_2$ (3.5 equiv) at 0 °C and stirred for indicated time at 0 °C.
[b] Isolated yield after silica gel column chromatography. Values in the parentheses indicate the yield of recovered starting material.
[c] α:β ratio was determined after isolation of each isomer.

product **5c** in 93% yield (α:β=10:90), which is, as expected, similar to the case of using ethyl 4,6-dimphenylpyrimidin-2(1*H*)-one-carboxylate (**2a**). Stirring with pyrimidin-2(1*H*)-one (**2b**–**c**) for 24 h at 0 °C provided product **5b**–**c** (α:β=0:100 (22%), α:β=6:94 (67%), respectively). The ratio of the products might be affected by the nucleophile size in the reaction with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl fluoride. However, the α-isomer was not obtained in all cases using 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**4a**) as the substrate (entries 4–6). In the case of fluoro saccharide (**4b**), defluorination proceeded so fast that the nucleophile attacked the oxocarbenium ion before coordination of the benzoyl group at the 2-position. The reaction was controlled mainly by steric hindrance of the oxocarbenium ion and nucleophile. On the other hand, in case of acetyl saccharide (**4a**), elimination of the leaving group was so slow that formation of oxocarbenium ion and coordination of the benzoyl group at the 2-position to the anomeric position occurred at the same time, leading to complete β-selectivity supported by the neighboring participation effect. Silylated pyrimidinone has higher reactivity than pyrimidinone itself, so the silylated pyrimidinone can only react with the oxocarbenium ion before coordination of the benzoyl group, affording the mixture of α- and β-isomer. On the other hand, the reaction with pyrimidinone itself is too slow and thus the coordination of the benzoyl moiety occurred prior to the oxocarbenium ion attack, affording only the β-isomer. We conclude that neighboring group participation by the benzoyl moiety at the 2-position does not always occur in the glycosidation reaction with fluoro saccharide. After the glycosidation, anomerization occurred, resulting in isolation of β-isomer predominantly. Thus, the reaction itself provided more α-isomer than the final yield. At least for the nucleoside having a possible leaving moiety at the anomeric center, we could assume that the final α:β ratio does not indicate the reaction selectivity.

Now, we will report the synthesis of novel nucleosides having a pyrimidin-2-thione moiety (Table 4). The present method is very simple compared with the silyl method described above.

The change between pyrimidin-2(1*H*)-ones and pyrimidin-2(1*H*)-thiones brought a significant effect to the nucleophilicity. In the case of pyrimidin-2(1*H*)-thiones, a silylation reagent is not essential for achieving good yield. Pyrimidin-2(1*H*)-thiones are more

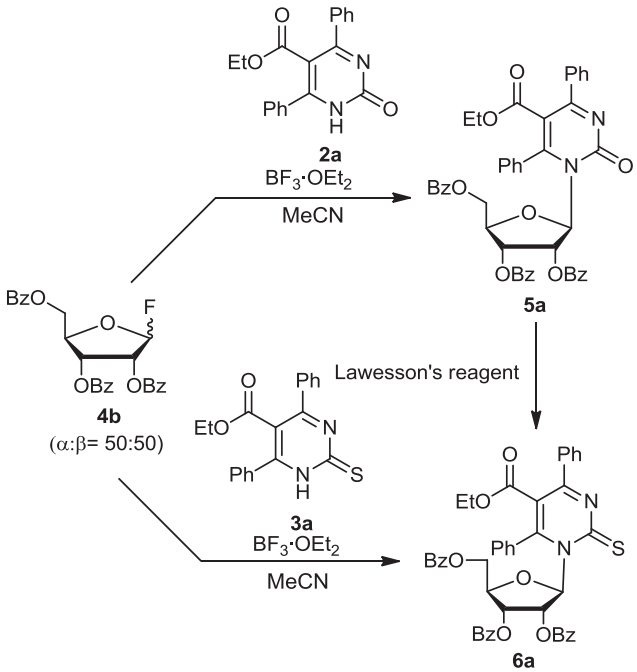
**Table 4**
Synthesis of novel nucleosides having a pyrimidin-2-thione moiety




| Entry[a] | $R^1$ | $R^2$ | Product | Yield/%[b] | α:β[c] |
|---|---|---|---|---|---|
| 1 | Ph | $CO_2Et$ | **6a** | 78 | β |
| 2 | Me | $CO_2Et$ | **6b** | 66 | β |
| 3 | Ph | H | **6c** | 47 | β |

[a] $BF_3·OEt_2$ (3.0 equiv) was added to a mixture of **4b** and **3a**–**c** (1.2 equiv) in MeCN and stirred for 1 h at 0 °C.
[b] Isolated yield after silica gel column chromatography. The values in the parentheses indicate the yield of the recovered starting material.
[c] α-Isomer was not obtained.

nucleophilic than pyrimidin-2(1*H*)-ones. Formation of *S*-glycoside and inversion of the tagging point between nitrogen and sulfur are unlikely to occur based on the additional experiment (Scheme 3) and other references.[4b,c] In all entries, the α-isomer was not observed. Using other pyrimidin-2(1*H*)-thiones, such as **3b** and **3c** provided the nucleosides in moderate yield. It is noteworthy that α-isomer was not observed under the above mentioned Vorbrüggen conditions using ethyl 4,6-diphenylpyrimidin-2(1*H*)-thione-5-carboxylate (**3a**) as the nucleobase.




**Scheme 3.** Determination of the nucleophilic atom in glycosidation.

In conclusion, we developed a non-metallic method for synthesizing novel nucleosides having a pyrimidin-2(1*H*)-one or pyrimidin-2(1*H*)-thione moiety. The silylated-method under Vorbrüggen conditions was not always required for the glycosidation with aromatic pyrimidin-2(1*H*)-ones and, especially,

thiones. We also showed and discussed the stereoselectivity in N-glycosidation due to the kinetics of 'neighboring group participation' and thermodynamics of 'anomerization'.

## 3. Experimental

### 3.1. General

All reactions were carried out in oven-dried glassware with magnetic stirring under an argon atmosphere unless otherwise mentioned. All starting materials were obtained from commercial sources and used without further purification unless otherwise stated. MS spectra were recorded using Thermo Quest LCQ DECA XP$^{plus}$. High resolution mass spectra (HRMS) were measured by JEOL JMS-T100LP AccuTOF LC-Plus (ESI). Melting points, which were uncorrected were recorded using Yanaco MP-500D. $^1$H and $^{13}$C NMR spectra (JEOL JNM-LA, 400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 using $Me_4Si$ as the internal standard (0 ppm). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Optical rotations were measured on a HORIBA SEPA-300 Polarimeter for solution in a 1 dm cell. IR spectra were measured with a Thermo SCIENTIFIC NICOLET iS 5. Elemental analyses were performed with a Yanaco CHN Corder MT-5.

### 3.2. General procedure to synthesize nucleosides having a pyrimidin-2-one moiety

To a MeCN solution (3 mL) of 2,3,5-tri-*O*-benzoyl-D-*ribo*-furanosyl fluoride as the substrate (0.8 mmol) was added ethyl 4,6-diphenylpyrimidin-(1*H*)-one-5-carboxylate (1.0 mmol) and BSA (1.9 mmol). The mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. $BF_3\cdot OEt_2$ (3.0 mmol) was added to the mixture slowly and stirred for 1 h, followed by quenching with satd $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and then filtered and evaporated. The residue was chromatographed on silica gel with hexane/ethyl acetate ratios of 7:1 and then 3:1 as the eluent to afford product **5a**.

*3.2.1. 1-(2′,3′,5′-Tri-O-benzoyl-α-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-diphenylpyrimidin-2-one (**α-5a**).* 91 mg (15%), colorless solid, mp 68–69 °C; $[\alpha]_D^{28}$ −0.04 (*c* 0.5, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 2979, 1722, 1536, 1450, 1410, 1249, 1093, 1062, 1025, 707; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.94 (t, *J*=7.0 Hz, 3H, $OCH_2CH_3$), 3.9–4.1 (m, 2H, $OCH_2CH_3$), 4.6–4.7 (m, 2H, *H*5; *H*5′), 4.85–4.90 (m, 1H, *H*4), 6.09 (d, *J*=4.8 Hz, 1H, *H*2), 6.15 (dd, *J*=4.8, 7.2 Hz, 1H, *H*3), 6.94 (s, 1H, *H*1), 7.2–7.7 (m, 17H, Ar*H*), 7.89 (d, *J*=0.8 Hz, 3H, Ar*H*), 8.04–8.07 (m, 4H, Ar*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 13.4, 61.9, 63.9, 71.5, 75.3, 76.7, 77.0, 79.9, 101.2, 121.2, 128.3, 128.4, 128.5, 128.5, 128.5, 128.8, 129.0, 129.1, 129.5, 129.6, 129.8, 129.9, 129.9, 130.3, 132.9, 133.4, 133.6, 137.2, 162.3, 165.0, 165.2, 166.2, 167.5, 167.9; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{45}H_{36}N_2NaO_{10}$: 787.2268 [M+Na]$^+$. Found: 787.2268.

*3.2.2. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-diphenylpyrimidin-2-one (**β-5a**).* 478 mg (78%), colorless solid, mp 171–172 °C (from THF/hexane); $[\alpha]_D^{28}$ −1.28 (*c* 1.0, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 2978, 2338, 2058, 1722, 1665, 1594, 1482, 1255, 712, 701; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.74 (t, *J*=7.4 Hz, 3H, $OCH_2CH_3$), 3.74 (q, *J*=6.9 Hz, 2H, $OCH_2CH_3$), 4.59–4.63 (m, 1H, *H*4), 4.78 (ddd, *J*=19.3, 11.9, 5.5 Hz, 2H, *H*5; *H*5′), 5.51 (d, *J*=2.0 Hz, 1H, *H*1), 6.19 (dd, *J*=7.6 Hz, *J*=7.6 Hz, 1H, *H*3), 6.32 (dd, *J*=2.0 Hz, *J*=6.8 Hz, 1H, *H*2), 7.2–7.8 (m, 17H, Ar*H*), 7.73 (dd, *J*=8.0, 8.0 Hz, 4H, Ar*H*), 7.93 (d, *J*=7.2 Hz, 2H, Bz*H*), 8.08 (d, *J*=6.8 Hz, 2H, Bz*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 13.3, 61.6, 64.4, 72.4, 74.2, 76.7, 77.0, 80.6, 94.2, 95.5, 113.6, 128.2, 128.2, 128.3, 128.3, 128.4, 128.7, 128.8, 129.0, 129.2, 129.5, 129.7, 129.9, 130.2, 130.6, 131.1, 133.0, 133.3, 133.5, 137.3, 153.8, 158.6, 165.0, 165.5, 165.5, 166.3, 172.2; MS [ESI$^+$] *m*/*z* 787.1 [M+Na]$^+$. Anal. calcd for $C_{45}H_{36}N_2O_{10}$: C, 70.67; H, 4.74; N, 3.66. Found: C, 70.33; H, 4.75; N, 3.68.

*3.2.3. 1-(2′,3′,5′-Tri-O-benzoyl-α-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-dimethylpyrimidin-2-one (**α-5b**).* 52 mg (27%), colorless solid; mp 80–81 °C; $[\alpha]_D^{28}$ −1.05 (*c* 0.5, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1720, 1451, 1315, 1262, 1177, 1091, 1067, 1025, 705; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.31 (t, *J*=6.4 Hz, 3H, $OCH_2CH_3$), 2.44 (s, 3H, *Me*), 2.31 (s, 3H, *Me*), 4.37 (q, *J*=6.8 Hz, 2H, $OCH_2CH_3$), 4.63–4.72 (m, 1H, *H*4), 4.82–4.87 (m, 2H, *H*5; *H*5′), 5.68 (d, *J*=2.0 Hz, 1H, *H*1), 6.05–6.28 (m, 2H, *H*2; *H*3), 7.3–7.5 (m, 9H, Ar*H*), 7.9–8.1 (m, 6H, Ar*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 14.0, 16.8, 61.3, 64.3, 64.5, 71.1, 71.6, 72.6, 75.0, 76.7, 77.0, 79.1, 84.3, 88.3, 91.2, 95.4, 97.0, 101.5, 109.8, 111.3, 128.3, 128.4, 128.4, 129.7, 129.8, 129.8, 132.9, 133.2, 137.0, 139.9, 150.6, 163.5, 165.0, 165.2, 165.4, 165.6, 166.0, 166.2; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{35}H_{32}N_2NaO_{10}$: 663.1955 [M+Na]$^+$. Found: 663.1953.

*3.2.4. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-dimethylpyrimidin-2-one (**β-5b**).* 120 mg (63%), colorless solid; mp 162–163 °C (from EtOAc/hexane); $[\alpha]_D^{28}$ +6.57 (*c* 0.5, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1718, 1674, 1602, 1515, 1451, 1263, 1097, 1024, 708; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.39 (t, *J*=7.2 Hz, 3H, $OCH_2CH_3$), 2.45 (s, 3H, *Me*), 2.48 (s, 3H, *Me*), 4.37 (q, *J*=7.2 Hz, 2H, $OCH_2CH_3$), 4.71 (dd, *J*=5.8 Hz, *J*=10.2 Hz, 1H, *H*4), 4.77–4.86 (m, 2H, *H*5; *H*5′), 5.97 (d, *J*=2.0 Hz, 1H, *H*1), 6.15 (d, *J*=1.8 Hz, *J*=7 Hz, 1H, *H*2), 6.24 (dd, *J*=7.0, 7.0 Hz, 1H, *H*3), 7.2–7.6 (m, 9H, Ar*H*), 7.85 (d, *J*=7.6 Hz, 2H, Ar*H*), 8.92 (d, *J*=7.2 Hz, 2H, Ar*H*), 8.07 (d, *J*=7.2 Hz, 2H, Ar*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 14.1, 17.5, 25.0, 62.0, 64.5, 72.5, 75.1, 76.7, 77.0, 80.7, 92.7, 113.5, 128.3, 128.4, 128.5, 128.7, 129.0, 129.7, 129.8, 129.8, 133.1, 133.4, 133.7, 153.8, 156.0, 165.1, 166.1, 166.2, 166.3, 174.1; MS [ESI$^+$] *m*/*z* 663.1 [M+Na]$^+$. Anal. calcd for $C_{35}H_{32}N_2O_{10}$: C, 65.62; H, 5.03; N, 4.37. Found: C, 65.47; H, 4.92; N, 4.10.

*3.2.5. 1-(2′,3′,5′-Tri-O-benzoyl-α-D-ribo-pentofuranosyl)-4,6-diphenylpyrimidin-2-one (**α-5c**).* 19 mg (9%), colorless solid; mp 60–61 °C; $[\alpha]_D^{28}$ +0.06 (*c* 0.5, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1722, 1587, 1533, 1451, 1092, 1069, 972, 764, 705; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.65–4.77 (m, 2H, *H*5; *H*5′), 4.88–4.92 (m, 1H, *H*4), 6.16 (d, *J*=4.8 Hz, 1H, *H*2), 6.20 (dd, *J*=4.8 Hz, 7.4 Hz, 1H, *H*3) 7.02 (s, 1H, *H*1), 7.2–7.6 (m, 8H, Ar*H*), 7.84 (s, 1H, Ar*H*), 7.9–8.1 (m, 7H, Ar*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 64.6, 72.6, 74.6, 76.7, 77.0, 80.6, 93.9, 103.5, 128.1, 128.3, 128.7, 128.8, 128.9, 129.0, 129.4, 129.7, 129.7, 129.8, 130.5, 132.3, 133.0, 133.2, 133.4, 135.7, 155.8, 160.0, 165.0, 166.3; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{42}H_{32}N_2NaO_8$: 715.2056 [M+Na]$^+$. Found: 715.2057.

*3.2.6. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-4,6-diphenylpyrimidin-2-one (**β-5c**).* 194 mg (84%), colorless solid; mp 99–100 °C (from THF/hexane); $[\alpha]_D^{28}$ −28.0 (*c* 1.0, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1718, 1674, 1602, 1515, 1451, 1263, 1097, 1024, 708; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.68 (dd, *J*=5.6, 12.8 Hz, 1H, *H*4), 4.79–4.87 (m, 2H, *H*5; *H*5′), 5.72 (d, *J*=1.6 Hz, 1H, *H*1), 6.27 (dd, *J*=7.2, 7.2 Hz, 1H, *H*3), 6.31 (dd, *J*=2.0, 8.0 Hz, 1H, *H*2), 6.75 (s, 1H, Ar*H*), 7.2–7.6 (m, 17H, Ar*H*), 7.71 (d, *J*=7.2 Hz, 2H, Ar*H*), 7.93 (d, *J*=7.6 Hz, 2H, Bz*H*), 8.04 (d, *J*=8.0 Hz, 2H, Bz*H*) 8.17 (d, *J*=6.0 Hz, 2H, Bz*H*); $^{13}$C NMR (100.4 MHz, $CDCl_3$): $\delta$ 64.6, 72.6, 74.6, 76.7, 77.0, 80.6, 93.9, 103.5, 128.1, 128.3, 128.7, 128.8, 128.9, 129.0, 129.4, 129.7, 129.7, 129.8, 130.5, 132.3, 133.0, 133.2, 133.4, 135.7, 155.8, 160.0, 165.0, 166.3; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{42}H_{32}N_2NaO_8$: 715.2056 [M+Na]$^+$. Found: 715.2056.

### 3.3. General procedure to synthesize nucleosides having a pyrimidin-2-thione moiety

To a MeCN solution (3 mL) of 2,3,5-tri-*O*-benzoyl-β-D-*ribo*-furanosyl fluoride as the substrate (0.5 mmol) was added ethyl 4,6-

diphenylpyrimidin-2(1*H*)-thione-5-carboxylate (0.6 mmol) and the solution was cooled to 0 °C. $BF_3 \cdot OEt_2$ (1.5 mmol) was added slowly to the mixture and stirred at 0 °C for 1 h, followed by quenching with satd $NaHCO_3$. The mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and then filtered and evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate ratios of 15:1 and then 7:1 as the eluent to afford product **6a**.

*3.3.1. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-diphenylpyrimidin-2-thione (**β-6a**).* 304 mg (78%), colorless needle, mp 102–104 °C (from EtOAc/hexane); $[\alpha]_D^{30}$ +21.8 (*c* 1.0, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1722, 1515, 1491, 1263, 1214, 1092, 1069, 1057, 864, 697; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.91 (t, *J*=7.2 Hz, 3H, $OCH_2CH_3$), 4.01 (q, *J*=7.2 Hz, 2H, $OCH_2CH_3$), 4.57 (dd, *J*=11.4, 3.5 Hz, 1H, *H*5), 4.7–4.8 (m, 2H, *H*4; *H*5′), 6.01 (dd, *J*=6.8, 5.0 Hz, 1H, *H*3), 6.14 (dd, *J*=5.0, 2.4 Hz, 1H, *H*2), 6.56 (d, *J*=2.4 Hz, 1H, *H*1), 7.2–7.6 (m, 19H, Ar*H*), 7.86 (d, *J*=8.0 Hz, 2H, Ar*H*), 7.98 (d, *J*=7.2 Hz, 2H, Ar*H*), 8.11 (d, *J*=7.2 Hz, 2H, Ar*H*); $^{13}C$ NMR (100.4 MHz, $CDCl_3$): $\delta$ 13.39, 61.87, 63.74, 71.74, 79.64, 86.13, 121.2, 128.4, 128.8, 129.1, 129.5, 129.7, 129.9, 130.2, 133.2, 133.3, 133.4, 137.0, 164.8, 165.0, 165.2, 166.2, 167.6, 169.6; MS [ESI$^+$] *m*/*z*: 781 $[M+H]^+$. Anal. calcd for $C_{45}H_{36}N_2O_9S$: C, 69.22; H, 4.65; N, 3.59. Found: C, 68.86; H, 4.71; N, 3.93.

*3.3.2. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-5-(ethoxycarbonyl)-4,6-dimethylpyrimidin-2-thione (**β-6b**).* 217 mg (66%), white solid, mp 62–63 °C; $[\alpha]_D^{26}$ +24.3 (*c* 1.0, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1719, 1262, 1225, 1092, 1068, 1024, 705, 686; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (t, *J*=6.9 Hz, 3H, $OCH_2CH_3$), 2.48 (s, 6H, *Me*), 4.40 (q, *J*=6.9 Hz, 2H, $OCH_2CH_3$), 4.56 (dd, *J*=12.0, 4.4 Hz, 1H, *H*5), 4.67–4.78 (m, 2H, *H*4; *H*5′), 5.97 (dd, *J*=7.0, 5.0 Hz, 1H, *H*3), 6.08 (dd, *J*=4.8, 2.8 Hz, 1H, *H*2), 6.45 (d, *J*=2.8 Hz, 1H, *H*1), 7.30–7.59 (m, 9H, Ar*H*), 7.88 (d, *J*=7.2 Hz, 2H, Ar*H*), 8.03 (d, *J*=7.6 Hz, 2H, Ar*H*), 8.09 (d, *J*=7.2 Hz, 2H, Ar*H*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ 14.10, 22.92, 30.88, 61.69, 63.82, 71.92, 75.96, 76.69, 77.00, 77.32, 79.73, 85.98, 122.7, 128.33, 128.38, 128.4, 128.8, 129.1, 129.5, 129.7, 129.8, 133.1, 133.4, 133.5, 164.9, 165.2, 165.4, 166.2, 167.0, 169.0; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{35}H_{32}N_2O_9S$: 679.1726 $[M+Na]^+$. Found: 679.1726.

*3.3.3. 1-(2′,3′,5′-Tri-O-benzoyl-β-D-ribo-pentofuranosyl)-4,6-diphenylpyrimidin-2-thione (**β-6c**).* 138 mg (47%), white solid, mp 163–164 °C (from MeCN); $[\alpha]_D^{27}$ +17.3 (*c* 1.0, $CHCl_3$); IR (KBr): $\upsilon$ ($cm^{-1}$) 1582, 1564, 1510, 1494, 1436, 1365, 1233, 1139, 746, 686; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.61 (dd, *J*=4.2, 12.2 Hz, 1H, *H*5), 4.81–4.71 (m, 2H, *H*4; *H*5′), 6.07 (dd, *J*=7.0, 4.8 Hz, 1H, *H*3), 6.18 (dd, *J*=4.8, 2.7 Hz, 1H, *H*2), 6.70 (d, *J*=2.7 Hz, 1H, *H*1), 7.30–7.61 (m, 12H, Ar*H*), 7.82 (s, 1H, Ar*H*), 7.90 (d, *J*=7.2 Hz, 2H, Ar*H*), 8.04–8.14 (m, 11H, Ar*H*); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ 63.90, 71.88, 79.62, 86.11, 95.26, 108.9, 127.2, 128.3, 128.4, 128.5, 128.82, 128.88, 129.0, 129.2, 129.6, 129.7, 129.8, 129.9, 131.1, 133.1, 133.4, 133.5, 136.4, 165.0, 165.1, 165.2, 166.3, 169.9; HRMS [ESI$^+$]: *m*/*z* calcd for $C_{42}H_{32}N_2O_9S$: 731.1828 $[M+Na]^+$. Found: 731.1825.

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## Supplementary data

Detailed experimental procedures and characterization data ($^1H$, $^{13}C$, IR, mass spectrometry). Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.017.

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