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Highly stereoselective synthesis of 2′-deoxy-β-ribonucleosides via a 3′-(*N*-acetyl)-glycyl-directing group

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ABSTRACT

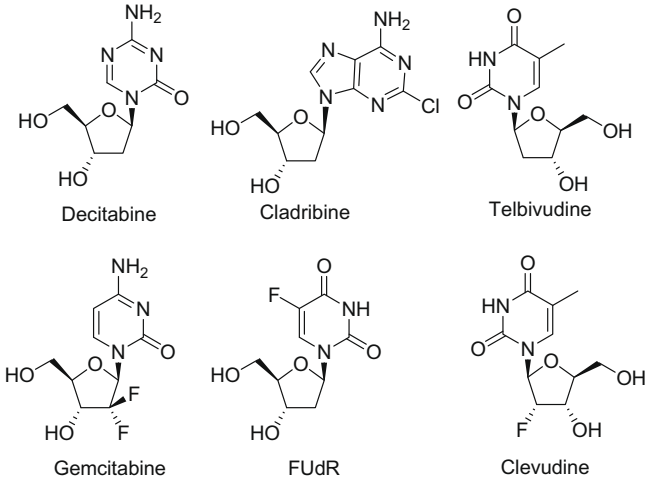
A facile synthesis of 2′-deoxy-β-ribonucleosides from 3′-*O*-(*N*-acetyl)-glycyl-protected 2′-deoxyribofuranose has been developed. The coupling reactions between the protected 2′-deoxyribose and silylated bases exhibited β-selectivity up to 98% presumably via a 1′,3′-participation mechanism. The 3′-directing group can be introduced and removed easily under mild conditions. This approach provides an efficient and highly stereoselective entry for the synthesis of 2′-deoxy-ribonucleosides.

Sugar–modified nucleoside analogs have been shown to exhibit potent antiviral and antitumor activities,[1] and a number of 2′-β-deoxyribonucleoside therapeutics have been in clinical use or under development such as Decitabine, Cladribine, and FUDR.[2] (Scheme 1). Ribonucleosides can be synthesized stereoselectively from acylated ribose and bases, and β-nucleosides are generally produced in high selectivity due to the participation of a neighboring group such as 2′-acyloxy group which shields the α-face from being attacked by a nucleobase (the Vorbrüggen Reaction).[3] However, in the case of 2′-deoxynucleosides, the Vorbrüggen method generally results in various ratios of β/α anomeric mixtures, which are often difficult to separate.[4]

To increase the β-stereoselectivity, a number of methods have been reported. Lipshultz's method used a pyrimidine base linked to the 5′ hydroxyl group of a 2′-deoxyriboside to improve the β-facial selectivity, but this method could only be applied to the pyrimidine nucleoside analogs.[5] Seela and Robins employed 2′-deoxy-3′,5′-di-*O*-(*p*-toluyl)-α-D-erylthropentofuranosyl chloride as the key intermediate for the synthesis of 2′-deoxy-β-ribonucleosides.[6] However, the instability of the chloride intermediate,[7] the low yield of the reaction, and the poor solubility of the heterocyclic base limited its applications.[8] Young[9] and Mukaiyama[10], respectively, adopted a similar strategy aiming to block the α-side of sugars from base attack by different 3′-thiocarbamate-directing groups. These reactions produced β-anomers with high stereoselectivities.[11] However, these 3′-thiocarbamate-directing groups were difficult to remove under mild conditions. There were also reports that 2′-deoxy-β-ribonucleosides could be synthesized via several selective 2′-deoxygenation of ribonucleosides in tedious steps.[12] Therefore, a practical synthetic method for the syntheses of 2′-deoxyribonucleosides with high β-selectivity is of great significance.

Herein, we report a facile and highly β-selective synthesis of 2′-deoxy-β-ribonucleosides through the coupling reaction of 3′-*O*-(*N*-acetyl)-glycyl-protected 2′-deoxyribofuranoses with silylated bases.

Given the fact that an ester group can be easily introduced and removed under mild conditions, we envisioned that the introduction of a substituted ester bearing electron donors in the ester chain as the directing group at *C*-3′ of the 2′-deoxy-ribofuranose



Scheme 1. Varieties of 2′-β-deoxynucleosides as drugs.

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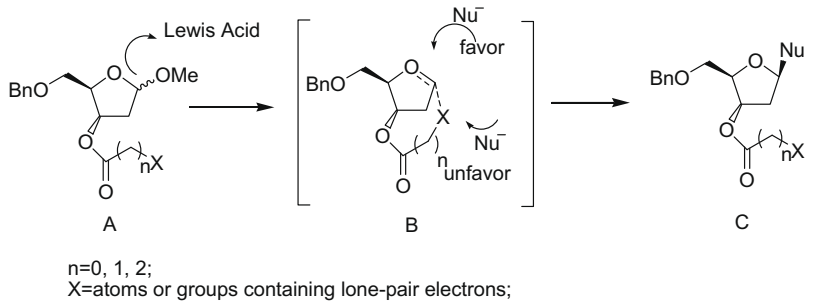
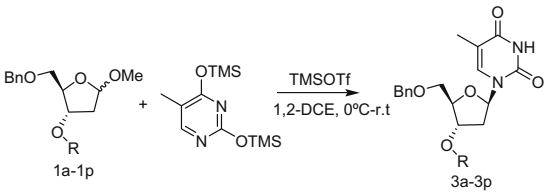


Scheme 2. The proposed mechanism of glycosylation via a 1′,3′-participation.

could stabilize the oxonium intermediate, thus leading to high β-selectivity through a tentative 1′, 3′-participation mechanism (Scheme 2) similar to what was proposed by Mukaiyama.[11]

To test this proposal, a series of 3′-directing group was screened. 5′-*O*-benzyl-1′-*O*-methyl-ribofuranosides were used as glycosyl donors (**1a–p**) (Table 1), which can be prepared through

Table 1
The glycosylation reactions of silylated pyrimidine with 2′-deoxyriboses



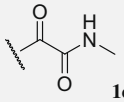
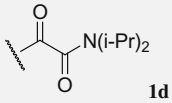
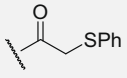
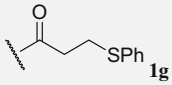
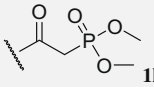
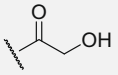
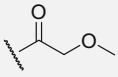
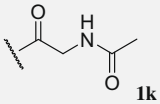
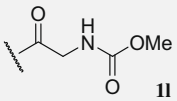
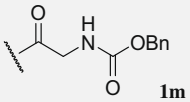
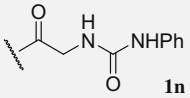
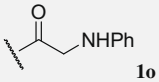
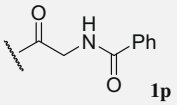
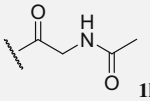
Entry	R	Time	β/α	Product/yield (%)
1	 **1a**	8 h	40/60	**3a**/72
2	 **1b**	8 h	40/60	**3b**/83
3	 **1c**	8 h	80/20	**3c**/61
4	 **1d**	8 h	75/25	**3d**/54
5	 **1e**	8 h	82/18	**3e**/83
6	 **1f**	8 h	80/20	**3f**/43
7	 **1g**	8 h	56/44	**3g**/63

Table 1 (*continued*)

Entry	R	Time	β/α	Product/yield (%)
8	 **1h**	8 h	71/29	**3h**/59
9	 **1i**	8 h	86/14	**3i**/78
10	 **1j**	8 h	84/16	**3j**/83
11	 **1k**	8 h	92/8	**3k**/88
12	 **1l**	12 h	87/13	**3l**/80
13	 **1m**	8 h	73/27	**3m**/41
14	 **1n**	8 h	88/12	**3n**/65
15	 **1o**	10 h	83/17	**3o**/73
16	 **1p**	8 h	80/20	**3p**/65
17	 **1k**	72 h, −78 °C	95/5	**3k**/36

The ratios of β/α isomers were determined by ^{1}H NMR of crude reaction mixtures.

esterification of the 2′-deoxyribose and various carboxylic acids. A number of solvents and catalysts were tested, and best result was obtained with 1,2-dichloroethane as the solvent[13] and TMSOTf as the catalyst.[14] The coupling reactions between a series of 3′-acyl-5′-benzyl-1′-*O*-methyl ribofuranosides (Table 1, entries 1–17, β/α = 50/50∼20/80) and silylated thymidine were studied at 0 °C. These coupling reactions gave β/α anomeric selectivities ranging from 60/40 to 95/5 (Table 1, entries 1–17).

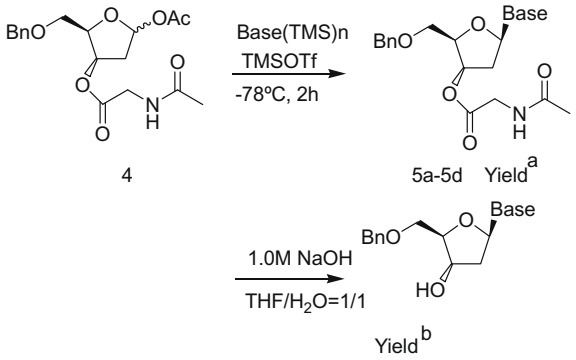
Similar to the literature reports,[7,8] we obtained low β-selectivity (β/α = 40/60) when **R** was acetyl or benzoyl, which was rationalized by the lack of stabilizing effect of the oxonium ion by the acetyl or benzoyl group (Scheme 1). Two oxalic acid derivatives were prepared as the directing group and the β-selectivities were improved but still moderate (Table 1, entries 3 and 4). The moderate selectivity may be due to the rigidity of the oxalyl side chains which could increase conformation restrain when forming the oxonium bridge. Further efforts were made to use more flexible chains as the directing groups. It was also found that chains containing *S* or *P* atom lead to low yields and low β-selectivities (Table 1, entries 5–8). We also prepared the xanthate analogs[9,10] (Table 1, entry 5), and the selectivity was modest. When the side chains were α-hydroxy acetyl and α-methoxy acetyl (Table 1, entries 9 and 10), the β-selectivities and yields were improved significantly. Finally, a series of substituted α-amine or α-amide esters as the directing groups were screened. When the directing group was *N*-acetyl-glycinate, the β-selectivity and yield were significantly improved (Table 1, entry 11). Other N-protected groups (Table 1, entries 12–16) led to lower β-selectivities. These poor selectivities (Table 1, entries 7 and 8 and entries 14–16) may be due to the misalignment of the lone pair electrons and the oxonium ion intermediate.

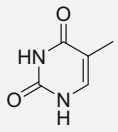
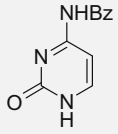
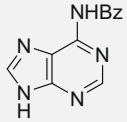
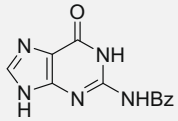
Based on the above results, we believed that 3′-*O*-*N*-acetyl-glycinate was a suitable directing group for the nucleo-glycosylation of 2′-deoxyribofuranses. Further study was conducted to investigate the influence of temperature. When **1k** was coupled with silylated thymidine, 72 h was needed for the reaction to be completed at −78 °C in a low yield (Table 1, entry 17). Then 5′-*O*-Benzyl-1′-*O*-acetyl-ribofuranose **4** was used for the coupling reaction because AcO is a better *C*-1′-leaving group at −78 °C, and the β-selectivity was improved remarkably (β/α = 98/2, Table 2, entry 1). It is worth noting that the reaction could be completed within 2 h.[9] To further investigate the scope of this method, we examined the reactions with different heterocyclic bases including N^4-benzoylcytosine, N^6-benzoyladenine, and N^2-benzoyl-guanine. All the coupling reactions provided high β-selectivities and good yields (Table 2).

These 3′-protected 2′-deoxynucleosides were readily hydrolyzed to give the corresponding nucleosides in excellent yields (**5a**–**d**, Table 2) upon treatment with a 1.0 M NaOH solution (Table 2).

In summary, a facile and efficient method for highly diastereoselective preparation of 2′-deoxy-β-ribonucleosides has been developed using the 3′-*O*-(*N*-acetyl)-glycinate as the protecting and directing group of the 2′-deoxyribofuranose. This method provides a highly selective and high-yielding glycosylation entry for the synthesis of 2-deoxy-β-nucleosides and its analogs.

Table 2
glycosylation reaction with different heterocyclic bases



Entry	Base	β/α	Product/ yield[a] (%)	Product/ yield[b] (%)
1		98/2	**5a**/82	**6a**/95
2		96/4	**5b**/71	**6b**/90
3		95/5	**5c**/83	**6c**/87
4		92/8	**5d**/73	**6d**/90

Yield[a], see Ref. 15.
Yield[b], isolated yields.

Acknowledgments

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15. *Typical procedure for the preparation of* **3k** is as follows:*Typical procedure for the preparation of* **3k** is as follows: (1): Preparation of trimethylsilylated thymine **2** in situ: To a solution of $(NH_4)_2SO_4$ (6 mg, 0.05 mmol) in 1,2-dichloroethane (2.0 mL) were added thymine (63 mg, 0.5 mmol) and HMDS (201 mg, 1.25 mmol) under N_2 atmosphere, and the mixture was refluxed for 2 h.(2): To the solution of trimethylsilylated thymine **2** was added a solution of

glycosyl donor (as a α and β mixture) (Table 1, entry 11, 135 mg, 0.4 mmol) in 1,2-dichloroethane (2.0 mL) under N_2 atmosphere, and the mixture was refluxed for 1 h. The reaction mixture was cooled to 0 °C for 0.5 h, and then a solution of TMSOTf (277 mg, 1.25 mmol) 1,2-dichloroethane solution (3.0 mL) was added slowly at 0 °C. The mixture was stirred at rt for 8 h, and then cooled to 0 °C, and quenched with saturated $NaHCO_3$ aqueous solution and filtered. The filtrate was extracted with dichloromethane (5 mL) for three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered and evaporated under reduced pressure to give **3k** (141 mg, 82% yield) as a colorless oil. The ratio of β/α isomers was calculated based on the ^{1}H NMR.*Selected data for compound* **3k** (as a α and β mixture): ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.01 and 9.93 (2 br s, 1H), 7.58 and 7.50 (2s, 1H), 7.33–7.29 (m, 5H), 6.49 and 6.31 (2 dd, 1H, J = 5.6, 2.4 and 6.0, 2.0 Hz), 5.48 and 5.35 (2 d, 1H, J = 6.4 Hz), 4.63–4.55 (m, 2H), 4.21–4.05 (m, 2H), 3.96–3.84 (m, 1H), 3.60–3.46 (m, 2H), 2.79–2.74 (m, 1H), 2.26–2.19 (m, 1H), 1.94–1.85 (4s, 6H); ESI-MS m/z (432, M+H$^+$), (454, M+Na$^+$).