Simple Synthesis of Aromatic β-C-Nucleosides via Coupling of Aryl Grignard Reagents with Sugar Fluorides

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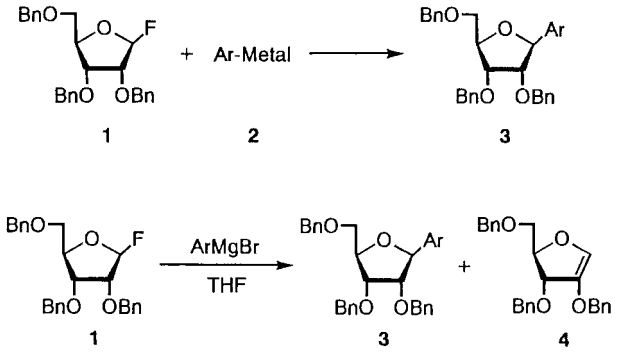
Abstract: The perbenzylated D-ribofuranosyl fluoride is allowed to react with Grignard reagents of aromatic heterocycles such as thiophene, pyrrole, and indole in THF to afford the corresponding β-*C*-nucleosides in moderate yields. The present process can be also applied to perbenzylated D-glucopyranosyl fluoride and perbenzylated 2-deoxy-D-ribofuranosyl fluoride as sugar donors.

Key words: sugar fluorides, Grignard reagents, *C*-nucleosides, β-selectivity

Since the remarkable biological activity of naturally occurring showdomycin was recognized, the synthesis of *C*-nucleosides has attracted wide interest in the field of organic chemistry.[1] In our study on the use of D-ribofuranosyl fluoride as a sugar donor,[2] we found that aryl Grignard reagents reacted easily with perbenzylated D-ribofuranosyl fluoride without Lewis acids to give the corresponding *C*-nucleosides in a β-selective manner. Recently, Kool and co-workers reported a procedure to prepare aromatic *C*-nucleosides using protected D-deoxyribosyl chloride as a sugar donor.[3] We wish to report here a better and practical method for the β-selective synthesis of *C*-nucleosides by utilizing the sugar fluorides in place of the unstable sugar chlorides (Scheme 1).



Scheme 1

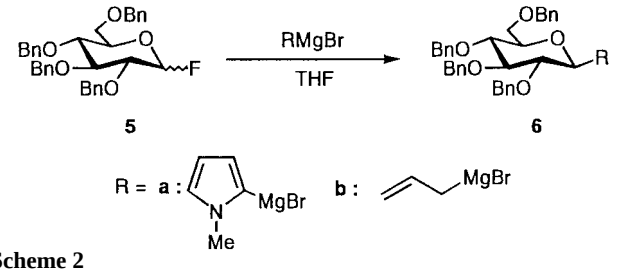
In a typical experimental procedure, a mixture of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl fluoride (**1**), 2-thienylmagnesium bromide **2**, and anhydrous THF was stirred at room temperature to afford the corresponding *C*-nucleoside **3** in 65 % yield in a β-selective manner (α/β = 8:92) (Scheme 1 and Table 1).

The solvent effect of the reaction was examined by changing diethyl ether to tetrahydrofuran as the solvent. Although diethyl ether was found to be a little better than THF in β-selectivity (Entry 3), THF was employed as the solvent due to easier handling. The β-selectivity was diminished when other metal reagents of heterocycles such as zinc and cadmium were used[4] (Entries 4–7). It is noticeable that Entry 6 shows α-selectivity (Scheme 2).

Table 1. Reaction of Sugar Fluoride **1** with Various Arylmetal Reagents **2**

Entry	Ar-Metal[a]	Solvent	Temp (°C)	Product	Yield (%)	Ratio of α/β
l	ArMgBr	THF	r.t.	**3a**	65	8:92
2	ArMgBr	THF	50	**3a**	52	0:100
3	ArMgBr	Et_2O	r.t.	**3a**	64	6:94
4	ArZnCl	THF	50	**3a**	67	18:82
5	Ar_2Zn	THF	50	**3a**	51	12:88
6	ArCdCl	THF	50	**3a**	53	58:42
7	Ar_2Cd	THF	50	**3a**	41	32:68
8	ArMgBr	THF	r.t.	**3b**	54	0:100

[a] For entries 4–7, Ar = 2-thienyl; for entry 8, Ar = *N*-methylpyrrol-2-yl.



Scheme 2

The reaction of arylmagnesium reagents with the sugar fluoride **1** was also examined. The reaction took place at room temperature to give the desired *C*-nucleosides with β-selectivity, while the yield of **3** increased at 50 °C together with perbenzylated D-ribofuranoid glycals **4** as byproducts (Scheme 1, Table 2). From Entries 2–5 it is clear that the electron-rich benzene derivatives afford more glycals **4**. The fact that the reaction with *p*-methoxyphenylmagnesium bromide gave glycal **4** in 44 % yield without the desired *C*-nucleoside, and the result of Entry 6 support this result.

Table 2. Reaction of Sugar Fluoride **1** with Various Aryl Grignard Reagents (ArMgBr)

Entry	Ar	Temp (°C)	Product(s)	Yield (%)
			3[a]	**4**
1	Ph	r.t.	23	0
2	Ph	50	57	29
3	2-MeC_6H_4	50	29	0
4	4-MeC_6H_4	50	45	51
5	3-$MeOC_6H_4$	50	34	36
6	4-ClC_6H_4	50	70	0
7	1-naphthyl	50	54	0

[a] Only β-selectivity was observed.

Table 3. IR and MS Data of Compounds **3–8** Prepared

Product[a]	Molecular Formula	IR (Neat) ν (cm^{-1})	HRMS (FAB/NBA), *m/z*	
			calc.	found
3a[b]	$C_{30}H_{30}O_4S$ (486.6)	1080, 2830	509.1763 ($M + Na^+$)	509.1763 ($M + Na^+$)
3b	$C_{31}H_{33}NO_4$ (483.6)	910, 1460, 1500, 2860, 3030	484.2488 (M + 1)	484.2501 (M + 1)
3c	$C_{32}H_{32}O_4$ (480.6)	700, 1460, 1500, 2940, 3020	519.1938 ($M + K^+$)	519.1954 ($M + K^+$)
3d	$C_{33}H_{34}O_4$ (494.6)	740, 1120, 2860, 2920, 3030	533.2094 ($M + K^+$)	533.2111 ($M + K^+$)
3e	$C_{33}H_{34}O_4$ (494.6)	700, 1100, 1150, 2950, 3010	533.2094 ($M + K^+$)	533.2106 ($M + K^+$)
3f	$C_{33}H_{34}O_5$ (510.6)	1090, 1130, 1460, 2880, 3030	549.2043 ($M + K^+$)	549.1997 ($M + K^+$)
3g	$_{32}H_{31}ClO_4$ (515.1)	1450, 1490, 1720, 2880, 3030	515.1989 (M + 1)	515.1986 (M + 1)
3h	$C_{36}H_{34}O_4$ (530.7)	1090, 1130, 1460, 2880, 3030	569.2094 ($M + K^+$)	569.2104 ($M + K^+$)
6a	$C_{39}H_{41}NO_5$ (603.8)	700, 1060, 2910, 3030, 3450	603.3063 (M)	603.3052 (M)
6b	$C_{37}H_{40}O_5$ (564.7)	1100, 2870, 2900, 3030, 3060	565.2954 (M + 1)	565.2944 (M + 1)
8a	$C_{23}H_{24}O_3S$ (380.5)	740, 1100, 1460, 2860, 3030	419.1083 ($M + K^+$)	419.1079 ($M + K^+$)
8b	$C_{27}H_{26}O_3S$ (430.6)	730, 1100, 2880, 2930, 3030	430.1603 (M)	430.1602 (M)

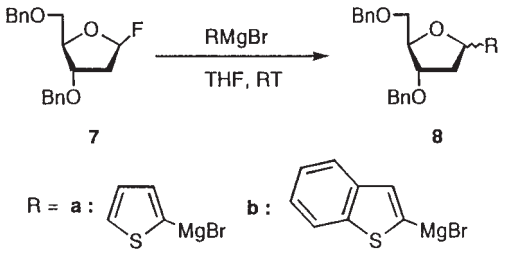
[a] All compounds are oils, except **3e**: mp 78–79 °C; **3g**: mp 54–56 °C; **6a**: mp 109–110 °C; and **8b**: mp 56–57 °C.
[b] Anal. calc. for $C_{30}H_{30}O_4S$ (486.6): C, 74.05; H, 6.21. Found: C, 73.90; H, 6.07.

Furthermore, the pyrrolylation and allylation of D-glucopyranose were successful by using the present procedure. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl fluoride (**5**)[5] was allowed to react with *N*-methylpyrrol-2-ylmagnesium bromide to give the corresponding product **6a** in 45 % yield as only β-epimer, and allylmagnesium bromide gave the corresponding product, **6b** in 77 % yield (α/β = 35:65).

The allylation of D-glucopyranose reported before gave the corresponding product in an α-selective manner.[6] Therefore, the sugar lactones have been employed in a two step procedure in order to obtain the corresponding β-glucosides.[7]

The structure determination of aromatic *C*-nucleosides was carried out by the comparison of their spectral data with those of authentic samples.[8] The stereochemistries of **3**, **6** and **8** were determined mainly by the result of differential NOE (1-H ↔ 4-H) and $J_{1'\,2'}$ values in NMR measurements. Particularly, the structure of **6b** was determined by the following NMR data; $J_{1'\,2'}$ values (α: 5.6 Hz, β: 12.5 Hz) and δ values in ^{13}C NMR of γ-position carbons to C-3 (α: 3′-C, δ = 82.4; 5′-C, δ = 71.2. β: 3′-C, δ = 87.3 ; 5′ -C, δ = 79.1). The IR, Mass, and ^1H NMR spectroscopic data are summarized in Tables 3 and 4.

The reaction of 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranosyl fluoride (7) with 2-thienylmagnesium bromide and 2-benzothienylmagnesium bromide afforded the corresponding products **8a** and **8b** in 37 (α/β = 67:33) and 54 % (α/β = 55:/45) yields, respectively (Scheme 3).



Scheme 3

The reaction is considered to proceed via an oxocarbenium ion, and show β-selectivity because of the steric hindrance of 2-alkoxy group. These are explained by the following facts:

(1) The α-epimer of **1** gave the same result as its β-epimer; (2) 2,3,5-tri-*O*-benzylribofuranose was observed in the first stage of the reaction by TLC monitoring; and (3) the use of 2,3,5-tri-*O*-methyl-D-ribofuranosyl fluoride in place of **1** gave the corresponding thiophenyl *C*-nucleoside in 49% yield with higher α-selectivity (α/β = 41:59) than that of **1**; (4) the use of **7** gave the corresponding product with α-selectivity.

The decrease of β-selectivity with softer zinc and cadmium reagents than a magnesium reagent[9] may be explained by the bulkiness of the nucleophilic species solvated strongly by THF even if the ionic adius of magnesium is smaller (Entries 1–7 in Table 1).[10]

Table 4. [1]H NMR Data of Compounds **3-8** Prepared

Product		[1]H NMR ($CDCl_3$/TMS)[h] δ, J (Hz)
3a	α-form	3.59–3.77 (m, 2 H, 5′-H_a, 5′-H_b), 4.03 (dd, 1 H, 2′-H, $J_{1',2'}$ = 3.3, $J_{2',3'}$ = 3.7), 4.24–4.28 (m, 2 H, 3′-H, 4′-H), 4.34–4.60 (m, 6 H, benzyl-H), 5.33 (d, 1 H, 1′-H, $J_{1',2'}$ = 3.3), 6,96–7.08 (m, 1 H, thiophene 4-H), 7.16 (d, 1 H, thiophene 3-H, $J_{3',4'}$ = 2.2), 7.18–7.20 (m, 1 H, thiophene 5-H), 7.22–7.33 (m, 15 H, benzyl Ph-H)
	β–form	3.60 (m, 2 H, 5′-H_a, 5′-H_b), 3.91 (dd, 1 H, 2′-H, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 5.0), 4.01 (dd, 1 H, 3′-H, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 3.8), 4.31 (dd, 1 H, 4′-H, $J_{3',4'}$ = 3.8, $J_{4',5'}$ = 4.4), 4.49–4.63 (m, 6 H, benzyl-H), 5.26 (d, 1 H, 1′-H, $J_{1',2'}$ = 6.6), 6.95 (m, 1 H, thiophene 4-H), 7.05 (m, 1 H, thiophene 3-H), 7.21–7.34 (m, 16 H, thiophene 5-H, benzyl Ph-H)
3b	β-form	3.52 (d, 2 H, 5′-H_a, 5′-H_b, $J_{4',5'}$ = 4.4), 3.58 (brs, 3 H, pyrrole NCH_3), 4.02 (dd, 1 H, 3′-H, $J_{2',3'}$ = 5.6), 4. 12 (dd, 1 H, 2′-H, $J_{1',2'}$ = 7.1, $J_{2',3'}$ = 5.6), 4.25–4.28 (m, 1 H, 4′-H), 4.46–4.66 (m, 6 H, benzyl-H), 5.02 (d, 1 H, 1′-H, $J_{1',2'}$ = 7.1), 6.02–6.05 (m, 2 H, pyrrole 3-H, 4-H), 6.57–6.58 (m, 1H, pyrrole 5-H), 7.22–7.34 (m, 15 H, benzyl Ph-H)
3c	β-form	3.61–3.69 (m, 2 H, 5′-H_a, 5′-H_b), 3.81 (dd, 1 H, 2′-H, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 5.4), 4.01 (dd, 1 H, 3′-H, $J_{2',3'}$ = 5.4, $J_{3',4'}$ = 4.6), 4.33–4.37 (m, 1 H, 4′-H), 4.44–4.63 (m, 6 H, benzyl-H), 5.02 (d, 1 H, 1′-H, $J_{1',2'}$ = 6.6), 7.17–7.40 (m, 20 H, benzene 2-H, 3-H, 4-H, 5-H, 6-H, benzyl Ph-H)
3d	β-form	2.37 (s, 3 H, Ar-CH_3), 3.65 (dd, 1 H, 5′-H_a, $J_{4',5'}$ = 3.9, J_{gem} = 10.5), 3.73 (dd, 1 H, 5′-H_b, $J_{4',5'}$= 3.9, J_{gem} = 10.5), 3.88 (dd, 1 H, 2′-H, $J_{1',2'}$ = 6.1, $J_{2',3'}$ = 5.6), 4.07 (t, 1 H, 3′-H, $J_{2',3'}$ = 5.6), 4.34 (q, 1 H, 4′-H, $J_{4',5'}$ = 3.9), 4.43–4.69 (m, 6 H, benzyl-H), 5.28 (d, 1 H, 1′-H, $J_{1',2'}$ = 6.1), 7.09–7.36 (m, 17 H, benzyl Ph-H, toluene-H), 7.50 (d, 2 H, toluene-H, J = 3.3)
3e	β-form	2.34 (s, 3 H, Ar-CH_3), 3.61–3.68 (m, 2 H, 5′-H_a, 5′-H_b), 3.80 (dd, 1 H, 2′-H, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 5.4), 4.00 (dd, 1H, 3′-H, $J_{2',3'}$ = 5.4, $J_{3',4'}$ = 4.6), 4.33 (dd, 1 H, 4′-H, $J_{3',4'}$ = 4.6, $J_{4',5'}$ = 4.0), 4.47–4.62 (m, 6 H, benzyl-H), 5.00 (d, 1 H, 1′-H, $J_{1',2'}$ = 6.6), 7.09–7.34 (m, 19 H, toluene 2-H, 3-H, 5-H, 6-H, benzyl Ph-H)
3f	β-form	3.61–3.68 (m, 5 H, 5′-H_a, 5′-H_b, Ar–OCH_3), 3.80–3.84 (m, 1 H, 2′-H, $J_{1',2'}$ = 6.3), 4.02 (t, 1 H, 3′-H), 4.33–4.36 (m, 1 H, 4′-H), 4.50–4.64 (m, 6 H, benzyl-H), 5.01 (d, 1 H, l′-H, $J_{1',2'}$ = 6.3), 6.79–6.82 (m, 1 H, anisole-H), 6.93–6.99 (m, 1 H, anisole-H), 7.19–7.66 (m, 17 H, benzyl Ph-H, anisole-H)
3g	β-form	3.60 (dd, 1 H, 5′-H_a, $J_{4',5'}$ = 3.8 Hz, J_{gem} = 10.3), 3.66 (dd, 1 H, 5′-H_b, $J_{4',5'}$ = 3.8, J_{gem} = 10.3), 3.74 (dd, 1 H, 2′-H, $J_{1',2'}$ = 7.=, $J_{2',3'}$ = 5.3), 3.99 (dd, 1 H, 3′-H, $J_{2',3'}$ = 5.3, $J_{3',4'}$ = 3.8), 4.34 (dd, 1 H, 4′-H, $J_{3',4'}$ = 3.8, $J_{4',5'}$ = 3.8), 4.38–4.69 (m, 6 H, benzyl-H), 4.97 (d, 1 H, 1′-H, $J_{1',2'}$ = 7.0), 6.98–7.37 (m, 19 H, chlorobenzene 2-H, 3-H, 5-H, 6-H, benzyl Ph-H),
3h	β-form	3.74 (dd, 1 H, 5′-H_a, $J_{4',5'}$ = 3.8 Hz, J_{gem} = 10.7), 3.86 (dd, 1 H, 5′-H_b, $J_{4',5'}$ = 3.4, Hz, J_{gem} = 10.7), 4.08 (t, 1 H, 2′-H, $J_{1',2'}$ = 4.8), 4.13–4.15 (m, 1 H, 3′-H), 4.43–4.68 (m, 7 H, 4′-H, benzyl-H), 5.78–5.79 (d, 1 H, 1′-H, $J_{1',2'}$ = 4.8), 7.19–7.42 (m, 18 H, naphthalene-H, benzyl Ph-H), 7.47 (dd, 1 H, naphthalene-H, J = 6.7, 7.0), 7.77 (dd, 1 H, naphthalene-H, J = 6.3, 6.8), 7.85 (d, 1 H, naphthalene-H, J = 8.7), 8.12 (d, 1 H, naphthalene-H, J = 8.5)
6a	β-form	3.55–3.58 (m, 1 H, 5′-H), 3.61 (s, 3 H, pyrrole NCH_3), 3.67–3.74 (m, 2 H, 2′-H, 4′-H), 3.75–3.79 (m, 3 H, 3′-H, 6′-H), 3.99 (d, 1 H, benzyl-H), 4.34 (d, 1 H, 1′-H, $J_{1',2'}$ = 9.5), 4.44–4.64 (m, 4 H, benzyl-H), 4.85–4.98 (m, 3 H, benzyl-H), 6.12–6.13 (m, 1 H, pyrrole 4-H), 6.24–6.26 (m, 1 H, pyrrole 3-H), 6.59–6.60 (m, 1 H, pyrrole 5-H), 7.01–7.36 (m, 20 H, benzyl Ph-H)
6b	α-form[b]	2.42–2.54 (m, 2 H, 3-H), 3.59–3.66 (m, 3 H, 4′-H, 5′-H, 6′-Ha), 3.70 (dd, 1 H, 6′-H_b, $J_{5',6'}$= 3.5, J_{gem} = 10.5), 3.75 (dd, 1 H, 2′-H, $J_{1',2'}$ = 5.6, $J_{2',3'}$ = 9.5), 3.79 (dd, 1 H, 3′-H, $J_{2',3'}$ =9.5, $J_{3',4'}$ = 8.1), 4.14 (ddd, 1 H, 1′-H, $J_{1',2'}$ = 5.6, $J_{1',3a}$ = 11.0, $J_{1',3h}$ = 4.6), 4.46–4.94 (m, 8H, benzyl-H), 5.07 (dd, 1 H, $J_{1,2}$ = 10.8, J_{gem} = 1.5), 5.15 (dd, 1 H, 1-H_b, $J_{1b,2}$= 17.1, J_{gem} = 1.5), 5.81 (dddd, 1 H, 2-H, $J_{1a,2}$ = 10.8, $J_{1b,2}$ = 17.1, $J_{2,3a}$ = 6.4, $J_{2,3b}$ = 7.3), 7.11–7.37 (m, 20 H, benzyl Ph-H)
	β-form[c]	2.32 (ddd, 1 H, 3-Ha, $J_{2,3a}$ = 7.1 Hz, J_{gem} = 14.6, $J_{1',3a}$ = 7.3), 2.60 (ddd, 1 H, 3-H_a, $J_{2,3b}$= 6.4, J_{gem} = 14.6, $J_{1',3b}$ = 3.2), 3.33 (dd, 1 H, 2′-H, $J_{1',2'}$ = 12.5, $J_{2',3'}$ = 8.3), 3.34 (ddd, 1 H, 1′-H, $J_{1',2'}$ = 12.5, $J_{1',3a}$ = 7.3, $J_{1',3b}$ = 3.2), 3.41 (ddd, 1 H, 5′-H, $J_{4',5'}$ = 9.6, $J_{5',6'a}$ = 4.5, $J_{5',6'b}$ = 2.0), 3.60 (dd, 1 H, 4′-H, $J_{3',4'}$ = 9.2, $J_{4',5'}$ = 9.6), 3.68 (dd, 1 H, 6′-Ha, $J_{5',6'a}$ = 4.5, J_{gem} = 10.6), 3.70 (dd, 1 H, 3′-H, $J_{2',3'}$ = 8.3, $J_{3',4'}$ = 9.2), 3.73 (dd, 1 H, 6′-H_b, $J_{5',6'b}$= 2.0, J_{gem} = 10.6), 4.55–4.90 (m, 8 H, benzyl-H), 5.07 (dd, 1 H, 1-H_a, $J_{1a,2}$= 10.3, J_{gem} = 1.0), 5.10 (dd, 1 H, 1-H_b, $J_{1b,2}$= 7.2, J_{gem} = 1.0), 5.93 (dddd, 1 H, 2-H, $J_{1a,2}$ = 10.3, $J_{1b,2}$ = 17.2, $J_{2,3a}$ = 6.4, $J_{2,3b}$ = 7. 1), 7.20–7.30 (m, 20 H, benzyl Ph-H)
8a	α-form	2.04–2.11 (m, 1 H, 2′-H_a, $J_{1',2'}$= 5.2), 2.41–2.44 (m, 1 H, 1-H_b, $J_{1',2'}$= 5.2), 3.53 (dd, 1 H, 5′-H_a, J_{gem} = 5.6, $J_{4'.5'}$ = 4.6), 3.65 (dd, 1 H, 5′-H_b, J_{gem} =5.6, $J_{4',5'}$ = 4.6), 4.17–4.19 (m, 1 H, 3′-H), 4.26–4.30 (m, 1 H, 4′-H), 4.52–4.62 (m, 4 H, benzyl-H), 5.39 (dd, 1 H, l′-H, $J_{1',2'}$ = 5.2), 6.94–7.01 (m, 3 H, thiophene 3-H, 4-H, 5-H) 7.23–7.36 (m, 10 H, benzyl Ph-H)
	β-form	2.17–2.26 (m, 1 H, 2′-H_a, $J_{1',2'}$= 6.7), 2.63–2.69 (m, 1 H, 2′-H_b, $J_{1',2'}$= 6.7), 3.59–3.67 (m, 2 H, 5′-H_a, 5′-H_b), 4.24–4.33 (m, 2 H, 3′-H, 4′-H), 4.47–4.62 (m, 4 H, benzyl-H), 5.34 (t, 1 H, 1′-H, $J_{1',2'}$ = 6.7), 6.94–7.02 (m, 3 H, thiophene 3-H, 4-H, 5-H), 7.24–7.37 (m, 10 H, benzyl Ph-H)
8b	α-form	2.27–2.33 (m, 1 H, 2′-H_a, $J_{1',2'}$= 6.7), 2.65–2.72 (m, 1 H, 2′-H_b, $J_{1',2'}$ = 6.7), 3.59–3.67 (m, 2 H, 5′-H_a, 5′-H_b), 4.28 (q, 1 H, $J_{3',4'}$ = 4.2, 3′-H), 4.37 (q, 1 H, $J_{3',4'}$ = 4.2, $J_{4',5'}$ = 8.4, 4′-H), 4.46–4.63 (m, 4 H, benzyl-H), 5.43 (t, 1 H, 1′-H, $J_{1',2'}$ = 6.7), 7.21–7.37 (m, 13 H, benzothiophene-H, benzyl Ph-H), 7.69 (d, 1 H, J=8.2, benzothiophene-H), 7.79 (d, 1 H, J=7.5, benzothiophene-H)
	β–form	2.11–2.18 (m, 1 H, 2′-H_a, $J_{1',2'}$= 5.3), 2.44–2.49 (m, 1 H, 2′-H_b, $J_{1',2'}$= 5.3), 3.54–3.58 (dd, 1 H, 5′-H_a, $J_{4',5'}$= 5.5, J_{gem} = 10.0), 3.68 (dd, 1 H, 5′-H_b, $J_{4',5'}$= 4.6, J_{gem} = 10.0), 4.20–4.22 (m, 1 H, 3′-H), 4.32–4.35 (m, 1 H, 4′-H, $J_{4',5'}$ = 5.5, 4.6), 4.54–4.65 (m, 4 HJ, benzyl-H), 5.45–5.49 (dd, 1 H, 1′-H, $J_{1',2'}$ – 5.3), 7.21–7.47 (m, 13 H, benzothiophene-H, benzyl Ph-H) 7.68–7.70 (dd, 1 H J = 7.4, benzothiophene-H), 7.79 (d, 1 H, J = 7.7, benzothiophene-H)

[a] [1]H NMR spectra were recorded at 400 MHz for **3b-h, 6a, 8a, b** and at 500 MHz for **3a, 6b.**
[b] [13]C NMR ($CDCl_3$/TMS): δ = 29.8 (3-C), 69.0 (6′-C), 71.52 (5′-C), 73.7 (1′-C), 78.2 (4′-C), 80. 1 (2′-C), 82.4 (3′-C), 116.8 (1-C), 134.8 (2-C)
[c] [13]C NMR ($CDCl_3$/TMS): δ = 36.0 (3-C), 69.1 (6′-C), 78.70 (4′-C), 78.74 (1′-C), 79.1 (5′-C), 81.6 (2′-C), 87.3 (3′-C), 117.0 (1-C), 134.8 (2 C).

In conclusion, the present method is very useful for the preparation of β-*C*-nucleosides, because sugar fluorides are very stable sugar donors and their glycosylation proceeds by simple operation and, furthermore, with β-selectivity.

2-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)thiophene (3a); Typical Procedure:

A mixture of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl fluoride (**1**; 85 mg, 0.2 mmol), 2-thienylmagnesium bromide (**2a;** 1.0 M THF solution, 2 mL, 2 mmol), and anhyd THF (2 mL) was stirred at r.t. for 3 h. The resulting mixture was quenched with H_2O, neutralized with aq NH_4Cl solution and extracted with $CHCl_3$ (4 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, which was purified by preparative TLC on silica gel (eluent: hexane/EtOAc, 4:1) to afford the corresponding *C*-nucleoside **3a** in 65 % yield (α/β = 8:/92). When 5 equiv of **2a** was used, the yield of **3a** decreased to 45 %. Thus 10 equiv of Grignard reagent was used in the reaction of **2a** and **2b.** In the cases of **2c–h**, the reaction was carried out with 5 equiv of the metal reagents.

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