Synthesis of C-Nucleosides Having Typical Aromatic Heterocycles as the Base Moiety

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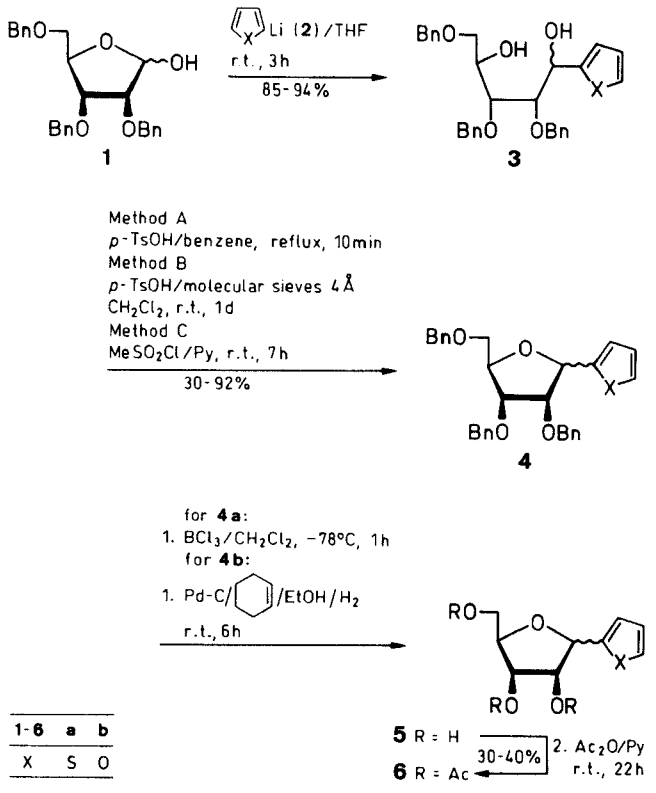
A 2,3,5-tri-*O*-benzyl-D-ribose reacts with lithium salts of thiophenes or furans to give the corresponding 2-ribosylthiophenes or furans, which are then treated with *p*-toluenesulfonic acid, affording 2-ribofuranosylthiophenes or furans (C-nucleosides) in good yield and in a stereoselective manner.

Recently, natural C-nucleosides have received considerable attention due to their remarkable antiviral and antitumor activities.[1] From this viewpoint we have developed new preparative methods of C-nucleosides[2] and, as a part of this study, we intended to synthesize the C-nucleosides having typical π-excess or π-deficient heterocycles as the base moiety. A systematic study of such type of nucleosides has not been published hitherto although fragmental reports appeared.[3]

In our preliminary experiment the desired nucleosides could not be obtained due to many side reactions by the direct reaction of a protected D-ribosyl bromide with lithium salts of aromatic heterocycles. Therefore another synthetic approach was required. Here we will present a synthetic procedure for C-nucleosides having furans or thiophenes as base moiety by using available lithium salts of aromatic heterocycles.[4]



Scheme 1

The reaction of protected D-ribose **1** with the lithium salt of heterocycle **2** or **7** gave the corresponding ribosyl-aromatic heterocycle **3** or **8**. Then, **3** or **8** could be cyclized to the corresponding ribofuranosyl-aromatic heterocycle **4** or **9** by treatment with *p*-toluenesulfonic acid in good yield with moderate stereoselectivity (Scheme 1 and 2).

The α- and β-forms of **4** and **9** were determined as follows: α-**4b** and β-**4b** were derived to the corresponding 2-(2,3-*O*-isopropylidene-α- and -β-ribofuranosyl)furans[3a] by the successive deprotection (Pd–C/H_2) and acetonation (2,2-dimethoxypropane/*p*-TsOH). The stereostructures of **4a**, **9a**, and **9b** were determined by their coupling constants of NMR ($J_{1',2'}$, $J_{2',3'}$, and $J_{3',4'}$) on comparison with those of **4b** (Table 4).

Next, the stereochemistry of **3** was established by their cyclization on treatment with methanesulfonyl chloride in pyridine to give α- and β-forms of **4**: an *R*/*S*-mixture of **3a** gave an α/β-mixture of **4a** with a ratio of 3:1; a *R*/*S*-mixture of **3b** gave an α/β-mixture of **4b** with a ratio of 3:2 (Table 1). These ratios coincided with those of two epimers (1'*R* and 1'*S*) of **3a** and **3b** judging from their 1'-proton's peak in ^{1}H NMR data (Table 4). Similarly, the stereochemistry of **8** was determined (Table 2).

Table 1. Compounds **3**, **4** and **6** Prepared

X	2	Products									
		3	(%)[a]	(*R*/*S*)	4	(%)[a]	(α/β)	Method	6	(%)[a]	(α/β)
S	**2a**	**3a**	94	3:1	**4a**	70	7:1	B	**6a**	30	1:8
					4a	92	1:8	A			
					4a	40	3:1	C			
O	**2b**	**3b**	85	3:2	**4b**	64	3:2	B	**6b**	40	1:3
					4b	85	1:3	A			
					4b	30	3:2	C			

[a] Isolated yield.

Table 2. Compounds **8**, **9** and **11** Prepared

X	7	Products									
		8	(%)[a]	(*R*/*S*)	9	(%)[a]	(α/β)	Method	11	(%)[a]	(α/β)
S	**7a**	**8a**	99	1:1	**9a**	95	2:1	A[b]	**11a**	40	2:1
					9a	33	1:1	C			
O	**7b**	**8b**	87	2:3	**9b**	87	2:3	A[b]	**11b**	80	2:3
					9b	42	2:3	C			

[a] Isolated yield.
[b] Time 1 h.

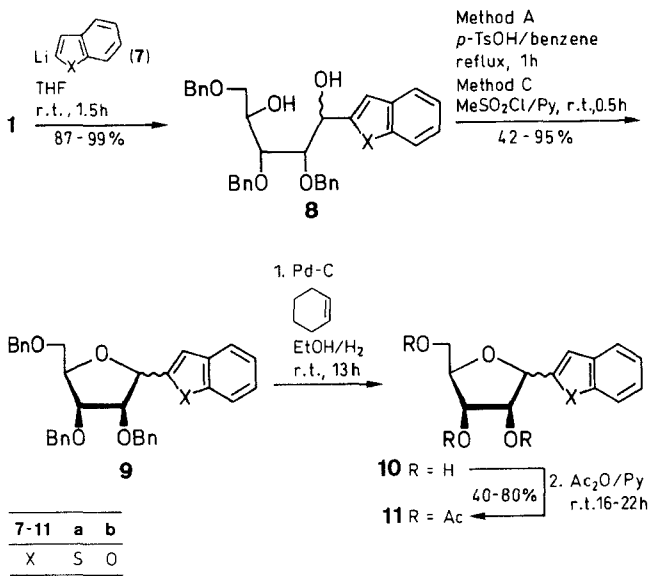
Table 3. Epimerization of **4** and **9**

Substrate	α/β	ΔG (kcal/mol)
4a	75:25 → 14:86	1.06
4b	60:40 → 25:75	0.64
9a	α → β	–
9b	40:60 → β	> 2.70

Table 4. Compounds **3–11** Prepared

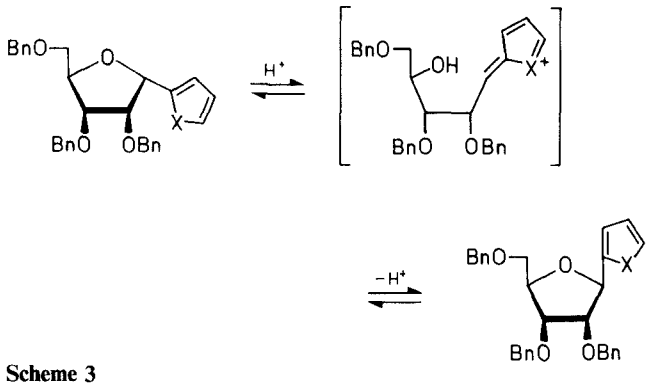
Product	Yield (%)[a]	Molecular Formula[b]	IR (neat) ν (cm^{-1})	MS (FAB, NBA) m/z	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	94	$C_{30}H_{32}O_5S$ (504.6)	3350, 2830, 1080	527 ($M + Na^+$)	2.63 [br d, 0.25H, 4'-OH (1'*S*), J = 4.1], 2.94 [br s, 0.75H, 4'-OH (1'*R*)], 3.52–3.97 (m, 5H, 2'-H, 3'-H, 4'-H, 5'-H), 4.02 [br s, 0.25H, 1'-OH (1'*S*)], 4.17–4.21 [br m, 0.75H, 1'-OH (1'*R*)], 4.44–4.66 (m, 6H, benzyl-H), 5.25 [d, 0.75H, 1'-H (1'*R*), $J_{1',2'}$ = 6.6], 5.30 [t, 0.25H, 1'-H (1'*S*), $J_{1',2'}$ = 4.1], 6.97–7.01 (m, 2H, thiophene 3,4-H), 7.17–7.34 (16H, thiophene 5-H, ph-H)
3b	85	$C_{30}H_{32}O_6$ (488.6)	3310, 2850, 1085	511 ($M + Na^+$)	3.29–4.20 (m, 7H, 2'-H, 3'-H, 4'-H, 5'-H, 1'-OH, 4'-OH), 4.34–4.69 (m, 6H, benzyl-H), 5.02 [d, 0.6H, 1'-H (1'*R*), $J_{1',2'}$ = 7.0], 5.05 [d, 0.4H, 1'-H (1'*S*), $J_{1',2'}$ = 4.0], 6.34–6.38 (m, 2H, furan 3,4-H), 7.15–7.40 (m, 16H, furan 5-H, ph-H)
(α)-**4a**	10	$C_{30}H_{30}O_4S$ (486.6)	2830, 1080	509 ($M + Na^+$)	3.59–3.77 (m, 2H, 5'-H), 4.03 (dd, 1H, 2'-H, $J_{1',2'}$ = 3.3, $J_{2',3'}$ = 3.7), 4.24–4.28 (m, 2H, 3'-H, 4'-H), 4.34–4.60 (m, 6H, benzyl-H), 5.33 (d, 1H, 1'-H, $J_{1',2'}$ = 3.3), 6.98–7.08 (m, 1H, thiophene 4-H), 7.16 (d, 1H, thiophene 3-H, $J_{3,4}$ = 2.2), 7.18–7.20 (m, 1H, thiophene 5-H), 7.22–7.33 (m, 15H, ph-H)
(β)-**4a**	82	$C_{30}H_{30}O_4S$ (486.6)	2830, 1080	509 ($M + Na^+$)	3.60 (d, 2H, 5'-H, $J_{4',5'}$ = 4.4), 3.91 (dd, 1H, 2'-H, $J_{1',2'}$ = 6.6, $J_{2',3'}$ = 5.0), 4.01 (dd, 1H, 3'-H, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 3.8), 4.31 (dd, 1H, 4'-H, $J_{3',4'}$ = 3.8, $J_{4',5'}$ = 4.4), 4.49–4.63 (m, 6H, benzyl-H), 5.26 (d, 1H, 1'-H, $J_{1',2'}$ = 6.6), 6.95 (dd, 1H, thiophene 4-H, J = 3.9, 4.9), 7.05 (m, 1H, thiophene 3-H), 7.21–7.34 (m, 16H, thiophene 5-H, ph-H)
(α)-**4b**	21	$C_{30}H_{30}O_5$ (470.6)	2840, 1095	493 ($M + Na^+$)	3.60 (dd, 1H, 5'a-H, J_{gem} = 8.0, $J_{4',5'a}$ = 3.0), 3.74 (dd, 1H, 5'b-H, J_{gem} = 8.0, $J_{4',5'b}$ = 2.8), 4.10–4.26 (m, 3H, 2'-H, 3'-H, 4'-H), 4.28–4.65 (m, 6H, benzyl-H), 5.12 (d, 1H, 1'-H, $J_{1',2'}$ = 3.6), 6.39 (dd, 1H, furan 4-H, J = 3.3, 1.9), 6.49 (m, 1H, furan 3-H), 7.21–7.42 (m, 16H, furan 5-H, ph-H)
(β)-**4b**	64	$C_{30}H_{30}O_5$ (470.6)	2840, 1095	493 ($M + Na^+$)	3.60 (d, 2H, 5'-H, $J_{4',5'}$ = 4.3), 4.04 (dd, 1H, 3'-H, $J_{2',3'}$ = 5.1, $J_{3',4'}$ = 4.7), 4.16 (dd, 1H, 2'-H, $J_{1',2'}$ = 6.0, $J_{2',3'}$ = 5.1), 4.28 (dd, 1H, 4'-H, $J_{3',4'}$ = 4.7, $J_{4',5'}$ = 4.3), 4.47–4.65 (m, 6H, benzyl-H), 5.03 (d, 1H, 1'-H, $J_{1',2'}$ = 6.0), 6.31–6.33 (m, 2H, furan 3,4-H), 7.16–7.37 (m, 16H, furan 5-H, ph-H)
6a	30	$C_{15}H_{18}O_7S$ (342.4)	2900, 1730	343 ($M + 1$)	2.03–2.13 (m, 9H, acetyl-H), 4.10–4.60 (m, 3H, 4'-H, 5'-H), 5.19–5.62 (m, 3H, 1'-H, 2'-H, 3'-H), 6.96–6.98 (m, 1H, thiophene 4-H), 7.00–7.03 (m, 1H, thiophene 3-H), 7.32–7.33 (m, 1H, thiophene 5-H)
6b	40	$C_{15}H_{18}O_8$ (326.3)	2900, 1730	327 ($M + 1$)	2.03–2.12 (m, 9H, acetyl-H), 2.89–3.03 (m, 2H, 5'-H), 4.13–5.50 (m, 4H, 1'-H, 2'-H, 3'-H, 4'-H), 6.06–6.27 (m, 1H, furan 4-H), 6.35–6.39 (m, 1H, furan 3-H), 7.26–7.31 (m, 1H, furan 5-H)
8a	99	$C_{34}H_{34}O_5S$ (554.7)	3100, 2800, 1080	555 ($M + 1$)	3.52–3.78 (m, 4H, 4'-H, 5'-H, 4'-OH), 4.01–4.11 (m, 3H, 2'-H, 3'-H, 1'-OH), 4.41–4.69 (m, 6H, benzyl-H), 5.31 [d, 0.5H 1'-H, (1'*R* or 1'*S*), $J_{1',2'}$ = 6.3], 5.35 [d, 0.5H 1'-H, (1'*R* or 1'*S*), $J_{1',2'}$ = 3.6], 7.12–7.37 (m, 18H, benzothiophene 3,5,6-H, ph-H), 7.68–7.83 (m, 2H, benzothiophene 4,7-H)
8b	97	$C_{34}H_{34}O_6$ (538.6)	3250, 2850, 1060	539 ($M + 1$)	2.70 (br s, 1H, 4'-OH), 3.51–3.78 (m, 3H, 4'-H, 5'-H), 4.10 (br s, 1H, 1'-OH), 4.20–4.28 (m, 2H, 2'-H, 3'-H), 4.36–4.69 (m, 6H, benzyl-H), 5.16–5.17 (m, 1H, 1'-H), 6.70 [s, 0.6H, benzofuran 3-H (1'*S*)], 6.73 [s, 0.4H, benzofuran 3-H (1'*R*)], 7.13–7.55 (m, 19H, benzofuran 4,5,6,7-H, ph-H)
(α)-**9a**	63	$C_{34}H_{32}O_4S$ (536.7)	2800, 1420, 1060	537 ($M + 1$)	3.62 (dd, 1H, 5'a-H, J_{gem} = 10.8, $J_{4',5'a}$ = 3.3), 3.77 (dd, 1H, 5'b-H, J_{gem} = 10.8, $J_{4',5'b}$ = 8.0), 4.14 (dd, 1H, 2'-H, $J_{1',2'}$ = 3.3, $J_{2',3'}$ = 3.8), 4.28 (dd, 1H, 3'-H, $J_{2',3'}$ = 3.8, $J_{3',4'}$ = 3.3), 4.29 (ddd, 1H, 4'-H, $J_{3',4'}$ = 3.3, $J_{4',5'a}$ = 3.3, $J_{4',5'b}$ = 8.0), 4.37–4.62 (m, 6H, benzyl-H), 5.37 (d, 1H, 1'-H, $J_{1',2'}$ = 3.3), 7.11–7.36 (m, 18H, benzothiophene 3,5,6-H, ph-H), 7.72 (d, 1H, benzothiophene 4-H, $J_{4,5}$ = 6.8), 7.82 (d, 1H, benzothiophene 7-H, $J_{6,7}$ = 7.7)
(β)-**9a**	32	$C_{34}H_{32}O_4S$ (536.7)	2800, 1420, 1060	537 ($M + 1$)	3.63 (dd, 2H, 5'-H, J_{gem} = 2.8, $J_{4',5'}$ = 4.0), 4.00 (dd, 1H, 2'-H, $J_{1',2'}$ = 6.3, $J_{2',3'}$ = 5.1), 4.04 (dd, 1H, 3'-H, $J_{2',3'}$ = 5.1, $J_{3',4'}$ = 4.0), 4.36 (ddd, 4'-H, $J_{3',4'}$ = 4.0, $J_{4',5'}$ = 4.0), 4.54–4.65 (m, 6H, benzyl-H), 5.33 (d, 1H, 1'-H, $J_{1',2'}$ = 6.3), 7.24–7.67 (m, 4H, benzothiophene 3,4,5,6-H, ph-H), 7.78 (d, 1H, benzothiophene 7-H, $J_{6,7}$ = 7.9)
(α)-**9b**[c]					
(β)-**9b**	87	$C_{34}H_{32}O_5$ (520.6)	2850, 1450, 1080	521 ($M + 1$)	3.65 (dd, 1H, 5'a-H, J_{gem} = 6.7, $J_{4',5'a}$ = 4.1), 3.71 (dd, 1H, 5'b-H, J_{gem} = 6.7, $J_{4',5'b}$ = 3.9), 4.12 (dd, 1H, 3'-H, $J_{2',3'}$ = 5.2, $J_{3',4'}$ = 5.0), 4.26 (dd, 1H, 2'-H, $J_{1',2'}$ = 5.5, $J_{2',3'}$ = 5.2), 4.35 (ddd, 1H, 4'-H, $J_{3',4'}$ = 5.0, $J_{4',5'a}$ = 4.1, $J_{4',5'b}$ = 3.9), 4.53–4.65 (m, 6H, benzyl-H), 5.18 (d, 1H, 1'-H, $J_{1',2'}$ = 5.5), 6.70 (s, 1H, benzofuran 3-H), 7.07–7.49 (m, 19H, benzofuran 4,5,6,7-H, ph-H)
(β)-**11a**	40[d]	$C_{19}H_{20}O_7S$ (392.4)	2900, 1720, 1030	393 ($M + 1$)	2.10–2.15 (m, 9H, acetyl-H), 4.24–4.50 (m, 3H, 4'-H, 5'-H), 5.23–5.37 (m, 3H, 1'-H, 2'-H, 3'-H), 7.05–7.37 (m, 3H, benzothiophene 3,5,6-H), 7.72–7.82 (m, 2H, benzothiophene 4,7-H)
(β)-**11b**	80[e]	$C_{19}H_{20}O_8$ (376.4)	2900, 1720, 1015	377 ($M + 1$)	2.09, 2.11, 2.12 (s × 3, 3H × 3, acetyl-H), 4.22 (dd, 1H, 5'a-H, J_{gem} = 7.4, $J_{4',5'a}$ = 4.7), 4.36 (ddd, 1H, 4'-H, $J_{3',4'}$ = 5.2, $J_{4',5'a}$ = 4.7, $J_{4',5'b}$ = 3.3), 4.55 (dd, 1H, 5'b-H, J_{gem} = 7.4, $J_{4',5'b}$ = 3.3), 5.15 (d, 1H, 1'-H, $J_{1',2'}$ = 5.5), 5.44 (dd, 1H, 3'-H, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 5.2), 5.61 (dd, 1H, 2'-H, $J_{1',2'}$ = 5.5, $J_{2',3'}$ = 5.5), 6.67 (s, 1H, benzofuran 3-H), 7.20–7.32 (m, 2H, benzofuran 5,6-H), 7.46 (d, 1H, benzofuran 4-H, $J_{4,5}$ = 7.3), 7.55 (d, 1H, benzofuran 7-H, $J_{6,7}$ = 7.7)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ± 0.3, H ± 0.3.
[c] Pure (α)-**9b** could not be isolated.
[d] Conversion yield from (β)-**9a** obtained by epimerization.
[e] Conversion yield from (β)-**9b** obtained by epimerization.



Scheme 2

It was found that the ratios of α/β of **4** depended on the reaction conditions of cyclization. This fact suggests that the epimerization takes place in the acidic conditions (Scheme 3).



Scheme 3

Then, the experiments for epimerization of **4** and **9** were carried out by treatment with trifluoroacetic acid. The results are summarized in Table 3.

The ΔG values were calculated by the α/β ratio at room temperature. In the case of 2-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)furan, ΔG has been observed to be 1.27 kcal/mol,[3a] while the equilibrium ratio of methyl glucopyranoside is $\alpha/\beta = 65.8:32.7$, corresponding to $\Delta G = 0.43$ kcal/mol.[5]

Thus, α- and β-forms of **4** were produced by kinetic and thermodynamic controlled conditions, respectively. The same trend was observed for the stereoselectivities of **9**; that is, the kinetic controlled product is the α-form of **9** and the thermodynamic controlled product is the β-form of **9**.

The α- and β-forms of **4a**, **4b**, and **9a** could be separated by the usual column chromatography but those of **9b** were difficult to separate.

Deprotections of **4b** and **9** were carried out easily by the usual Pd–C-method. But, **4a** could only be deprotected by using boron trichloride in place of the above method. Thus obtained nucleosides **5** and **10** were confirmed as their acetyl derivatives **6** and **11**.

The present method could not be applied to pyrroles and pyridines as aromatic heterocycles, because their lithium salts did not react cleanly with **1**. However, this is a useful and convenient method to afford D-ribosyl- or D-ribofuranosylthiophenes and furans stereoselectively.

The lithium salts of aromatic heterocycles used here were prepared by the same method as that of 2-thienyllithium.[6] Spectroscopic data of compounds prepared are summarized in Table 4. Wakogel C-200 was used for column chromatography and Wakogel B-5F was used for preparative TLC (pTLC).

2-(2,3,5-Tri-*O*-benzyl-D-ribosyl)thiophene (3a); Typical Procedure:
To a solution of thiophene (126 mg, 1.5 mmol) in dry THF (2 mL) was added BuLi (hexane solution, 1.5 mmol) dropwise and the mixture was stirred at r.t. for 0.5 h. To the resultant yellow mixture was added a solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**1**; 210 mg, 0.5 mmol) in dry THF (1 mL) and then the mixture was stirred at r.t. for 3 h. The mixture was quenched with H_2O (5 mL) and 1 N HCl (5 mL), extracted with $CHCl_3$ (3 × 5 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed by pTLC on silica gel (eluent: EtOAc/hexane, 1:2, $R_f = 0.33$) to give **3a** in 94% yield; (1′*R*/1′*S*) 3:1.

2-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)thiophene (4a): Typical Procedures:
Method A: A mixture of **3a** (252 mg, 0.5 mmol), *p*-TsOH (5 mg), and benzene (20 mL) was refluxed for 10 min using azeotropic equipment. The mixture was condensed and purified by pTLC on silica gel (eluent: EtOAc/hexane, 1:2, $R_f = 0.7$); yield: 92% (α/β) 1:8.

Method B: A mixture of **3a** (252 mg, 0.5 mmol), *p*-TsOH (5 mg), molecular sieves 4 Å (2 g), and dry CH_2Cl_2 (3 mL) was stirred at r.t. for 1 d. After filtration the mixture was condensed and purified by pTLC on silica gel (eluent: EtOAc/hexane 1:2, $R_f = 0.7$); yield: 70%; (α/β) 7:1.

Method C ($MeSO_2Cl$ method): To a solution of **3a** (252 mg, 0.5 mmol) in pyridine (3 mL) was dropped $MeSO_2Cl$ (0.25 mL, 3 mmol) and the mixture was stirred at r.t. for 7 h. The mixture was quenched with 1 N HCl (5 mL), extracted with $CHCl_3$, and purified by pTLC on silica gel (eluent: EtOAc/hexane, 1:2) to give **4a** in 40% yield; (α/β) 3:1.

Deprotection of 2-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)benzofuran (9b); Typical Procedure:
A mixture of **9b** (262 mg, 0.5 mmol), 10% Pd–C (152 mg, 0.14 mmol), dry cyclohexene (2 mL), and dry EtOH (4 mL) was stirred under H_2 at r.t. for 13 h. The mixture was filtered through Celite and the filter pad was washed with EtOH. The combined filtrate and washings were evaporated under reduced pressure to give a syrupy trihydroxy form of **10b**, which was then stirred with dry pyridine (3 mL) and Ac_2O (0.7 mL) for 22 h. The mixture was quenched with aq NH_4Cl. Purification by pTLC on silica gel (eluent: EtOAc/hexane, 1:2, $R_f = 0.4$) gave **11b** in 80% yield.

Deprotection of 2-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)thiophene (4a):
To a solution of **4a** (80 mg, 0.17 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of 1 M BCl_3 in CH_2Cl_2 (0.8 mL, 0.8 mmol) at −78 °C. After stirring for 1 h at the same temperature, the mixture was added to dry MeOH/CH_2Cl_2 (1:1, 8 mL) and then neutralized with powder $NaHCO_3$ at r.t. The resulting mixture was filtered and washed with dry MeOH. The combined filtrate and washings were evaporated to give syrupy **5a**, which was further evaporated with dry MeOH (3 × 5 mL) and then stirred with dry pyridine (3 mL) and Ac_2O (0.7 mL) for 22 h. The mixture was

quenched with aq NH_4Cl. Purification by pTLC on silica gel (eluent: EtOAc/hexane, 1:2, $R_f = 0.4$) gave **6a** in 30% yield.

Epimerization of 9b; Typical Procedure:
A mixture of **9b** (129 mg, 0.25 mmol), CF_3CO_2H (0.3 mL), and CH_2Cl_2 (2 mL) was stirred at r.t. for 1 d. The mixture was quenched with aq $NaHCO_3$ to give the β-form of **9b** in 85% isolated yield.

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