Stereoselective coupling of riboses with metallic salts of aromatic heterocycles

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The coupling of 2,3,5-tri-*O*-benzyl-D-ribofuranose with the magnesium, cadmium and zinc salts of typical aromatic heterocycles can afford the corresponding β-*C*-nucleosides stereoselectively. Furthermore, the present method can be applied to the synthesis of β-*C*-deoxynucleosides having N-containing aromatic heterocycles as base moieties.

Introduction

Natural and unnatural *C*-nucleosides constitute an important class of organic compounds having significant therapeutic promise as antiviral, antitumour and anticancer agents.[1] Generally, their syntheses are multi-step, and are limited in applicability.[2] Previously we reported a simple method for *C*-ribonucleoside synthesis using the lithium salts of typical π-excessive and π-deficient aromatic heterocycles.[3] Here we report a method for the synthesis of predominantly β-*C*-nucleosides using the magnesium, cadmium and zinc salts of aromatic heterocycles.

Results and discussion

Our preliminary report[4] described a stereoselective synthesis of *C*-ribonucleosides starting from the reaction of 2,3-*O*-isopropylidene-5-*O*-D-ribofuranose **1** and the lithium salts of aromatic heterocycles, compounds **2**.

A typical example is shown in Scheme 1: the coupling of furanose **1** with lithium salt **2** afforded the corresponding D-*ribo*-pentitolyl heterocycles **3** in good yields. These products were then cyclized in a stereospecific manner under Mitsunobu conditions[5] followed by deprotection[6] to give the desired *C*-ribonucleosides in moderate yields. The results are summarized in Table 1.

The *R*- and *S*-epimers of compounds **3a–c** gave respective α-anomers and β-anomers of their cyclization products **4a–c** in a stereospecific manner, while the inverse relationship of **3d** to its product **4d** is due to the methodological protocols for determining absolute configuration (the 'Sequence Rules'). These results showed no predictable preference for the β-anomers more often found in Nature. Therefore we decided to examine other metal salts to see if a different stereoselection could be exploited.[7] As a preliminary experiment, 2,3,5-tri-*O*-benzyl-D-ribose **6** was treated with some metallic salts of thiophene, *N*-methylindole and pyridine. The results are shown in Table 2.

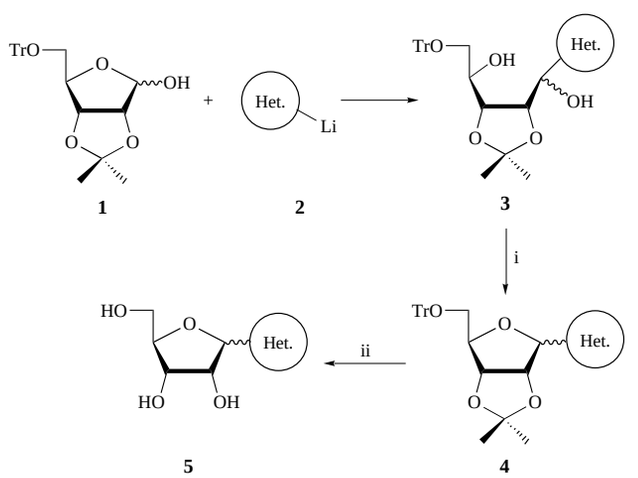
In all cases considered the less basic cadmium, zinc and magnesium salts gave the predominant stereochemistry leading to β-*C*-nucleosides. This stereoselectivity may be due to an easy *re*-plane attack of heterocycles on the carbonyl group of an intermediate metal chelate, as shown in structure **A** (Scheme 2).

Next, the 2,3-*O*-isopropylidene-protected compound **1** was coupled with the lithium and the magnesium salts of the heterocycles, compounds **7**. The results are shown in Table 3.

The magnesium salt of thiophene gave only the *R*-epimer of product **3**, while the *S*-epimer of compound **3** was obtained exclusively in the case of *N*-methylindole and pyridine. Therefore, only α-*C*-nucleosides can be obtained by using the magnesium salts **7**. This stereoselectively may be explained by a

Table 1 Synthesis of *C*-ribonucleoside

Heterocycle's base moiety	Isolated yield (%)					
	3 (*R*/*S*)		**4** (α/β)		**5** (α/β)	
2-Thienyl	**3a**	99 (4/3)	**4a**	79 (4/3)	**5a**	66 (4/3)
2-Benzothienyl	**3b**	91 (5/7)	**4b**	71 (5/7)	**5b**	82 (5/7)
2-Furyl	**3c**	97 (100/0)	**4c**	78 (100/0)	**5c**	65 (100/0)
2-Indolyl	**3d**	83 (8/1)	**4d**	93 (1/8)	**5d**	67 (1/8)



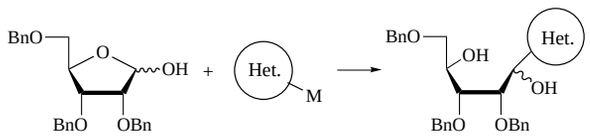
Scheme 1 *Reagents:* i, DEAD, PPh_3; ii, I_2, MeOH

nucleophilic attack on the carbonyl group proceeding exclusive *via* a more stable intermediate **B** (Scheme 2).

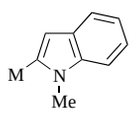
In the preparation of *C*-deoxyribonucleosides, we have previously reported a coupling reaction of 2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranose **9** with the lithium salts **7** of aromatic heterocycles.[8] The reaction proceeds in a *R*-stereoselective manner, resulting in the predominant formation of α-anomers of *C*-deoxyribonucleosides (Scheme 3).

In the same way as described for the D-ribose derivatives, the reaction of furanose **9** was performed with various metal salts **7**. The results are summarized in Table 4. As for the case with D-ribose derivatives, the cadmium and zinc salts showed predominant *S*-stereoselectivity, in contrast to the *R*-stereoselectivity of the lithium salts. The appearance of this stereoselection may be due to *re*-plane attack of the nucleophile on the carbonyl group of more stable intermediate **C**, as shown in Scheme 2. The following fact supports the presence of intermediate **C**. The intermediate chelate with magnesium, which was prepared from an equimolar mixture of compound **9** and

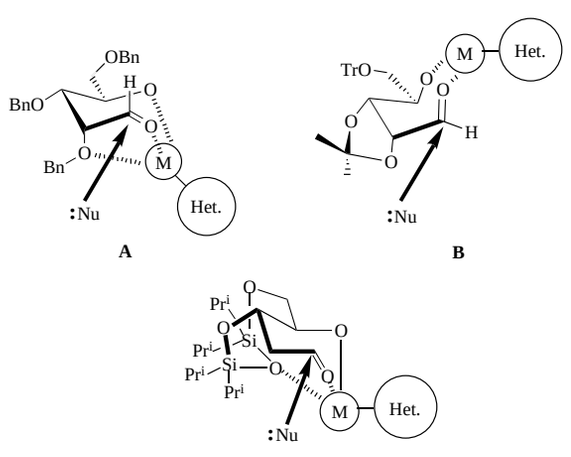
Table 2



6 **7** **8**

7	M [a]	Isolated yield (%) (*R*/*S*)
 **7a**	Li	94 (75/25)
	MgBr	93 (29/71)
	$CeCl_2$	19 (55/45)
	Cd	62 (6/94)
	Zn	50 (9/91)
 **7e**	Li	55 (50/50)
	MgBr	46 (85/15)
	$CeCl_2$	*b*
	Cd	59 (100/0)
	Zn	51 (100/0)
 **7f**	Li	31 (35/65)
	MgBr	69 (93/7)
	$CeCl_2$	*b*
	Cd	13 (100/0)
	Zn	*b*

[a] Cd, Zn reagents exist as Ar_2–Metal. [b] No reaction.



A **B** **C**

Scheme 2

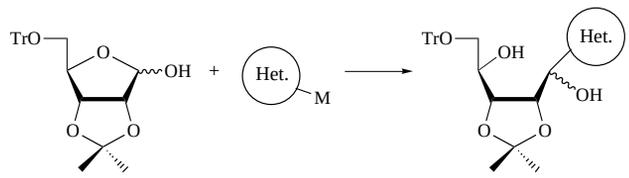
ethylmagnesium bromide, was allowed to react with 2-thienyllithium at −78 °C and afforded the corresponding addition product **10a** in 65% yield (*R*/*S* = 55/45), while the reaction of furanose **9** with 2-thienyllithium gave compound **10a** in 77% yield (*R*/*S* = 81/19) as shown in Table 4.

In conclusion, the reaction of furanose **6** with the cadmium, zinc and magnesium salts of aromatic heterocycles can lead to the corresponding β-*C*-ribonucleosides. Also, when compound **9** is coupled with the cadmium and zinc salts of aromatic heterocycles, the corresponding β-*C*-deoxyribonucleosides may be formed.

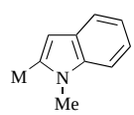
Experimental

IR spectra were recorded on a Hitachi 215 spectrometer. Mass spectra were obtained on Hitachi M-60 and JEOL-JMS-HX110 mass spectrometers. For fast-atom bombardment (FAB) mass spectra, NBA refers to *m*-nitrobenzyl alcohol matrix. ^{1}H NMR spectra were measured [$CDCl_3$ as a solvent (unless specified otherwise) using tetramethylsilane (TMS) as

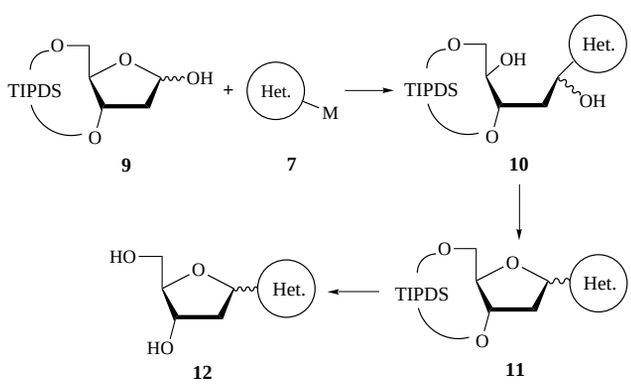
Table 3



1 **7** **3**

7	M	Isolated yield (%) (*R*/*S*)
 **7a**	Li	99 (4/3)
	MgBr	56 [85] [a] (100/0)
 **7e**	Li	23 (0/100)
	MgBr	34 [41] [a] (0/100)
 **7f**	Li	58 (0/100)
	MgBr	21 [46] [a] (0/100)

[a] Conversion yield.



9 **7** **10** **12** **11**

Scheme 3 TIPDS = tetraisopropyldisiloxane-1,3-diyl

internal reference] with JEOL-JNM-FX-270 and JNM-GSX-500 spectrometers. Chemical shifts are expressed in δ-values, and *J* values are given in Hz. 2D ^{1}H NMR (COSY and NOESY) data were measured with a JNM-GSX-500 spectrometer. Wakogel C-200 and C-300 were used for TLC and Wakogel B-5F for preparative TLC (PLC).

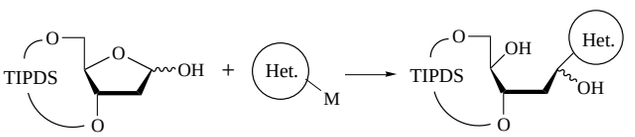
Preparation of 2-*ribo*-pentitol-1-yl-thiophene 3a, -benzothiophene 3b, and -furan 3c; typical procedure

To a solution of thiophene, benzothiophene or furan (1.5 mmol) in dry tetrahydrofuran (THF) was added BuLi (hexane solution; 1.5 mmol) dropwise during 5 min at 0 °C and the solution was stirred at room temperature for 0.5 h. The resultant yellow solution was added to a solution of 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranose **1** (0.5 mmol) in dry THF (5 cm^3) dropwise during 5 min at 0 °C and then the mixture was stirred at room temperature for 2 h before being quenched with water (5 cm^3) and neutralized with aqueous NH_4Cl (5 cm^3), extracted with $CHCl_3$ (3 × 10 cm^3) and the extract dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure and the residue was chromatographed by PLC on silica gel [developer: AcOEt–hexane (1:3)] to give product **3a**, **3b** or **3c**, respectively.

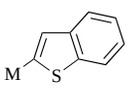
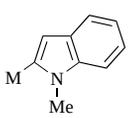
Preparation of the 2-*ribo*-pentitol-1-ylindole 3d

To a solution of indole (3.5 mmol) in dry THF (15 cm^3) was

Table 4



9 **7** **10**

7	M [a]	Isolated yield (%) (*R*/*S*)
 **7a**	Li	77 (81/19)
	MgBr	73 (53/47)
	$CeCl_2$	35 (100/0)
	Cd	37 (0/100)
	Zn	55 (19/81)
 **7b**	Li	71 (71/29)
	MgBr	68 (50/50)
	Cd	28 (24/76)
 **7e**	Li	70 (52/48)
	MgBr	48 (36/64)
	$CeCl_2$	40 (53/47)
	Cd	38 (25/75)
	Zn	59 (5/95)
 **7f**	Li	50 (70/30)
	MgBr	28 (33/67)
	Cd	32 (40/60)

[a] Cd, Zn reagents exist as Ar_2–Metal.

added BuLi (hexane solution; 3.5 mmol) dropwise during 5 min at −78 °C and the solution was stirred at room temperature for 30 min. Dry carbon dioxide gas was then passed into the solution for 10 min at −78 °C with vigorous stirring. After storage for 5–15 min at room temperature, the excess of carbon dioxide and THF were removed below 25 °C on a rotary evaporator attached to a vacuum pump, to give a solid. The flask was evacuated thoroughly, flushed with dry argon gas three times, and THF (20 cm^3) was added. The solution was cooled to −78 °C and then Bu^{t}Li (pentane solution; 3.8 mmol) was slowly added at the same temperature and the resultant yellow solution was stirred at the same temperature for 1.5 h. To this solution was slowly added a mixture of 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribose **1** (0.5 mmol) in dry THF (5 cm^3) and BuLi (hexane solution; 0.5 mmol) and the resultant red or orange solution was stirred and warmed slowly to room temperature during 4–5 h. After the disappearance of 2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribose monitored by PLC on silica gel, water (30 cm^3) was added for quenching, and then the solution was extracted with $CHCl_3$ (5 × 20 cm^3) and dried over anhydrous Na_2SO_4. The mixture was concentrated under reduced pressure at low temperature (< 20 °C) and the residue was chromatographed by PLC on silica gel [developer AcOEt–hexane (1:3)] to give compound **3d**.

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-*ribo*-pentitol-1-yl)thiophene 3a. Foam, ν_{max}(KBr)/cm^{-1} 700, 1070, 1220, 1340, 1440, 1485, 1590, 2900 and 3350; HRMS (FAB, NBA + NaCl) (Found: $C_{31}H_{32}NaO_5S$, M = 539.1866. Calc. for $C_{31}H_{32}NaO_5S$, M = 539.1866) (Found: C, 71.9; H, 6.5. $C_{31}H_{32}O_5S$ requires C, 72.1; H, 6.2%); δ_H(400 MHz; $CDCl_3$) (*R*-form) 1.26 (3 H, s, isopropylidene CH_3), 1.27 (3 H, s, isopropylidene CH_3), 3.28 (1 H, d, $J_{4',4'\text{-OH}}$ 2.8, 4′-OH), 3.33 (1 H, dd, $J_{4',5',a}$ 7.6, J_{gem} 9.8, 5′-H[a]), 3.56 (1 H, dd, $J_{4',5'b}$ 2.9, J_{gem} 9.7, 5′-H[b]), 4.03 (1 H, m, 4′-H), 4.18 (1 H, dd, $J_{2',3'}$ 5.2, $J_{3',4'}$ 9.9, 3′-H), 4.33 (1 H, dd, $J_{1',2'}$ 9.4, $J_{2',3'}$ 5.2, 2′-H), 4.59 (d, $J_{1',1'\text{-OH}}$ 3.0, 1′-OH), 5.11 (1 H, dd, $J_{1',1',OH}$ 3.0, $J_{1',2'}$ 9.4, 1′-H), 6.99 (1 H, dd, $J_{3,4}$ 3.6, $J_{4,5}$ 5.0, thiophene 3-H), 7.12 (1 H, d, $J_{3,4}$ 3.6 thiophene 3-H) and 7.25–7.46 (16 H, m, Ph and thiophene 5-H); (*S*-form) 1.38 (3 H, s, isopropylidene CH_3), 1.47 (3 H, s, isopropylidene CH_3), 2.65 (1 H, d, $J_{4',4'\text{-OH}}$ 5.1, 4′-OH), 3.11 (1 H, d, $J_{1',1'\text{-OH}}$ 7.5, 1′-OH), 3.33 (1 H, dd, $J_{4',5'a}$ 5.7, J_{gem} 9.6, 5′-H[a]), 3.42 (1 H, dd, $J_{4',5'b}$ 2.9, J_{gem} 9.6, 5′-H[b]), 4.19 (1 H, m, 4′-H), 4.26 (1 H, dd, $J_{2',3'}$ 6.2, $J_{3',4'}$ 9.2, 3′-H), 4.48 (1 H, dd, $J_{1',2'}$ 2.6, $J_{2',3'}$ 6.2, 2′-H), 5.35 (1 H, dd, $J_{1',1'\text{-OH}}$ 7.5, $J_{1',2'}$ 2.6, 1′-H), 6.97 (1 H, m, thiophene 4-H), 7.06 (1 H, m, thiophene 3-H) and 7.23–7.45 (16 H, m, Ph and thiophene 5-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-*ribo*-pentitol-1-yl)benzothiophene 3b. Foam, ν_{max}(KBr)/cm^{-1} 730, 800, 1070, 1200, 1360, 1430, 2850 and 3400; HRMS (FAB, NBA + KI) (Found: $C_{35}H_{34}KO_5S$, M = 605.1764. Calc. for $C_{35}H_{34}KO_5S$: M = 605.1764) (Found: C, 74.0; H, 5.8. $C_{35}H_{34}O_5S$ requires C, 74.2; H, 6.0%); δ_H(500 MHz; $CDCl_3$) (*R*-form) 1.26 (3 H, s, isopropylidene CH_3), 1.29 (3 H, s, isoproplylidene CH_3), 3.30 (1 H, br s, 4′-OH), 3.35 (1 H, dd, $J_{4',5',a}$ 7.4, J_{gem} 9.6, 5′-H[a]), 3.58 (1 H, dd, $J_{4',5',b}$ 2.9, J_{gem} 9.6, 5′-H[b]), 4.04 (1 H, ddd, $J_{3',4'}$ 5.2, $J_{4',5',a}$ 7.4, $J_{4',5',b}$ 2.9, 4′-H), 4.20 (1 H, dd, $J_{2',3'}$ 5.2, $J_{3',4'}$ 9.9, 3′-H), 4.38 (1 H, dd, $J_{1',2'}$ 9.4, $J_{2',3'}$ 5.2, 2′-H), 4.73 (1 H, br s, 1′-OH), 5.17 (1 H, d, $J_{1',2'}$ 9.4, 1′-H), 7.25–7.45 (18 H, m, Ph and benzothiophene 3-,5-,6-H) and 7.72–7.82 (2 H, m, benzothiophene 4-,-7-H); (*S*-form) 1.38 (s, 3 H, isopropylidene CH_3), 1.49 (3 H, s, isopropylidene CH_3), 2.72 (1 H, br s, 4′-OH), 3.25 (1 H, br s, 1′-OH), 3.35 (1 H, dd, $J_{4',5',a}$ 5.8, J_{gem} 9.6, 5′-H[a]), 3.43 (1 H, dd, $J_{4',5'b}$ 2.8, J_{gem} 9.6, 5′-H[b]), 4.21 (1 H, ddd, $J_{3',4'}$ 9.1, $J_{4',5'a}$ 5.8, $J_{4',5'b}$ 2.8, 4′-H), 4.29 (1 H, dd, $J_{2',3'}$ 6.3, $J_{3',4'}$ 9.1, 3′-H), 4.56 (1 H, dd, $J_{1',2'}$ 7.4, $J_{2',3'}$ 6.3, 2′-H), 5.44 (1 H, d, $J_{1',2'}$ 7.4, 1′-H), 7.25–7.45 (18 H, m, Ph-H and benzothiophene 3-,5-,6-H), 7.71–7.80 (2 H, m, benzothiophene 4-, 7-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-*ribo*-pentitol-1-yl)furan 3c. Foam, ν_{max}(Nujol)/cm^{-1} 1370, 1450, 2900 and 3350; HRMS (FAB, NBA) (Found: $C_{31}H_{32}O_6$, M = 500.2198; C, 74.1; H, 6.6. $C_{31}H_{32}O_6$ requires M = 500.2198; C, 74.4; H, 6.4%); δ_H(500 MHz; $CDCl_3$) (*R*-form) 1.24 (3 H, s, isopropylidene CH_3), 1.28 (3 H, s, isopropylidene CH_3), 3.32 (2 H, dd, $J_{4',5'a}$ 6.1, J_{gem} 9.9, 5′-H[a], 4′-OH), 3.55 (1 H, dd, $J_{4',5'b}$ 2.9, J_{gem} 9.9, 5-H[b]), 4.00 (1 H, m, 4′-H), 4.41 (1 H, dd, $J_{2',3'}$ 5.1, $J_{3',4'}$ 7.4, 3′H), 4.34 (1 H, br s, 1′-OH), 4.55 (1 H, dd, $J_{2',3'}$ 5.1, 2′-H), 4.90 (1 H, d, $J_{1',2'}$ 9.5, 1′-H), 6.36 (2 H, m, furan 3-, 4-H) and 7.23–7.46 (16 H, m, Ph and furan 5-H); (270 MHz; $CDCl_3$) δ_H(*S*-form) (270 MHz; $CDcl_3$) 1.37 (3 H, s, isopropylidene CH_3). 1.43 (3 H, s, isopropylidene CH_3), 2.58 (d, $J_{4',4'\text{-OH}}$ 5.3, 4′-OH), 2.92 (1 H, d, $J_{1',1'\text{-OH}}$ 7.9, 1′-OH), 3.32 (1 H, dd, $J_{4',5'a}$ 5.6, J_{gem} 9.6, 5′-H[a]), 3.41 (1 H, dd, $J_{4',5',b}$ 2.9, J_{gem} 9.6, 5′-H[b]), 4.13 (1 H, m, 4′-H), 4.24 (1 H, dd, $J_{2',3'}$ 6.3, $J_{3',4'}$ 9.2, 3′-H), 4.56 (1 H, dd, $J_{1',2'}$ 3.0, $J_{2',3'}$ 6.3, 2′-H), 5.13 (1 H, dd, $J_{1',1'\text{-OH}}$ 7.9, $J_{1',2'}$ 3.0, 1′-H), 6.35 (2 H, m, furan 3, 4-H) and 7.15–7.64 (16 H, m, Ph and furan 5-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethjyl-D-*ribo*-pentitol-1-yl)indole 3d. Foam, ν_{max}(KBr)/cm^{-1} 700, 750, 880, 900, 1060, 1150, 1210, 1280, 1335, 1375, 1440, 1480, 1580, 2900, 2950, 3020 and 3350; HRMS (FAB, NBA) (Found: $C_{35}H_{35}NO_5$, M = 549.2518; C, 76.2; H, 6.1; N, 2.7. $C_{35}H_{35}NO_5$ requires M = 549.2515; C, 76.5; H, 6.4; N, 2.6%); δ_H(400 MHz; $CDCl_3$) (*R*-form) 1.38 (3 H, s, isopropylidene CH_3), 1.49 (3 H, s, isopropylidene CH_3), 2.86 (1 H, d, $J_{4',4'\text{-OH}}$ 4.2, 4′-OH), 3.11 (1 H, d, $J_{1',1'\text{-OH}}$ 6.4, 1′-OH), 3.35 (1 H, dd, $J_{4',5'a}$ 5.8, J_{gem} 9.5, 5′-H[a]), 3.46 (1 H, dd, $J_{4',5'b}$ 2.7, J_{gem} 9.5, 5′-H[b]), 4.23 (2 H, m, 3′-, 4′-H), 4.49 (1 H, dd, $J_{1',2'}$ 2.8, $J_{2',3'}$ 5.5, 2′-H), 5.12 (1 H, d, $J_{1',\ 1'\text{-OH}}$ 6.4, $J_{1',2'}$ 2.8, 1′-H), 6.45 (1 H, s, indole 3-H), 7.05–7.58 (19 H, m, Ph and indole 4-, 5-, 6- and 7-H) and 8.80 (1 H, br s, indole 1-H).

2-(2,3-*O*-Isopropylidene-5-*O*′triphenylmethyl-D-*ribo*-pentitol-1-yl)-*N*-methyl indole 3e. Foam, ν_{max}(KBr)/cm^{-1} 730, 770, 1100, 1460, 1710, 2950 and 3400; HRMS (FAB, NBA) (Found: $C_{36}H_{37}NO_5$, M = 563.2639; C, 76.5; H, 6.3; N, 2.7. $C_{36}H_{37}NO_5$) requires M = 563.2672; C, 76.7; H, 6.6; N, 2.5%; δ_H(400 MHz; $CDCl_3$) (*S*-form) 1.23 (3 H, s, isopropylidene CH_3, 1.33 (3 H, s, isopropylidene CH_3), 3.32 (1 H, s, 4′-OH), 3.38 (1 H, dd, $J_{4',5',a}$

7.7, J_{gem} 9.9, 5′-H[a]), 3.60 (1 H, dd, $J_{4',5'b}$ 2.9, J_{gem} 9.9, 5′-H[b]), 3.82 (3 H, s, indole NCH_3), 4.01 (1 H, m, 4′-H), 4.24 (1 H, dd, $J_{2',3'}$ 5.1, 3′-H), 4.52 (1 H, br s, 1′-OH), 4.66 (1 H, dd, $J_{2',3'}$ 5.1, 2′-H), 5.13 (1 H, d, $J_{1',2'}$ 7.3, 1′-H), 6.55 (1 H, s, indole 3-H) and 7.04–7.50 (19 H, m, Ph and indole 4-, 5-, 6-, 7-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-ribofuranosyl)thiophene 4a. Foam, ν_{max}(KBr)/cm^{-1} 700, 760, 860, 900, 1025, 1070, 1200, 1360, 1440, 1480, 2880, 2960 and 3000; HRMS (FAB, NBA) (Found: $C_{31}H_{30}O_4S$, M = 498.1864; C, 74.9; H, 6.0. $C_{31}H_{30}O_4S$ requires M = 498.1866; C, 74.7; H, 6.1; δ_H(400 MHz; $CDCl_3$) (α-form) 1.33 (3 H, s, isopropylidene CH_3), 1.58 (3 H, s, isopropylidene CH_3), 3.24 (1 H, dd, $J_{4',5'a}$ 4.0 J_{gem} 10.0, 5′-H[a]), 3.35 (1 H, dd, $J_{4',5'b}$ 4.5, J_{gem} 10.0, 5′-H[b]), 4.32 (1 H, m, 4′-H), 4.83 (2 H, m, 2′-, 3′-H), 5.55 (1 H, d, $J_{1',2'}$ 2.9, 1′-H), 7.01–7.11 (2 H, m, thiophene 3-, 4-H), 7.23–7.45 (16 H, m, Ph and thiophene 5-H); δ_H(β-form) 1.33 (3 H, s, isopropylidene CH_3), 1.59 (3 H, s, isopropylidene CH_3), 3.22 (1 H, dd, $J_{4',5'a}$ 4.6, J_{gem} 10.0, 5′-H[a]), 3.37 (1 H, dd, $J_{4',5'b}$ 3.9, J_{gem} 10.0, 5′-H[b]), 4.26 (1 H, m, 4′-H), 4.68 (2 H, m, 2′-, 3′-H), 5.16 (1 H, dd, $J_{1',2'}$ 2.4, $J_{long\ range}$ 1.5, 1′-H), 6.99 (1 H, m, thiophene 4-H), 7.09 (1 H, m, thiophene 3-H) and 7.20–7.50 (16 H, m, Ph and thiophene 5-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-ribofuranosyl)benzothiophene 4b. Foam, ν_{max}(KBr)/cm^{-1} 700, 740, 1000, 1020, 1420, 2800 and 3000; HRMS (FAB, NBA) (Found: $C_{35}H_{32}O_4S$, M = 548.2026; C, 76.3; H, 6.0. $C_{35}H_{32}O_4S$ requires M = 548.2021; C, 76.6; H, 5.9%); δ_H(400 MHz; $CDCl_3$) (α-form) 1.33 (3 H, s, isopropylidene CH_3), 1.56 (3 H, s, isopropylidene CH_3), 3.26 (1 H, dd, $J_{4',5'a}$ 4.3, J_{gem} 10.2, 5′-H[a]), 3.40 (1 H, dd, $J_{4',5'b}$ 3.9, J_{gem} 10.2, 5′-H[b]), 4.38 (1 H, ddd, $J_{3',4'}$ 0.9, $J_{4',5'a}$ 4.3, $J_{4',5'b}$ 3.9, 4′-H), 4.85 (1 H, dd, $J_{2',3'}$ 6.0, $J_{3',4'}$ 0.9, 3′-H), 4.95 (1 H, dd, $J_{1',2'}$ 4.0, $J_{2',3'}$ 6.0, 2′-H), 5.63 (1 H, d, $J_{1',2'}$ 4.0, 1′-H), 7.25–7.46 (18 H, m, benzothiophene 3-, 5-, 6-H) and 7.75–7.84 (2 H, m, benzothiophene 4-, 7-H); δ_H(β-form) 1.34 (3 H, s, isopropylidene CH_3), 1.61 (3 H, s, isopropylidene CH_3), 3.25 (1 H, dd, $J_{4',5'a}$ 4.6, J_{gem} 10.3, 5′-H[a]), 3.39 (1 H, dd, $J_{4',5'b}$ 4.0, J_{gem} 10.3, 5′-H[b]), 4.32 (1 H, ddd, $J_{3',4'}$ 3.5, $J_{4',5'a}$ 4.6, $J_{4',5'b}$ 4.0, 4′-H), 4.71 (1 H, dd, $J_{2',3-}$ 6.6, $J_{3',4'}$ 3.5, 3′-H), 4.76 (1 H, dd, $J_{1',2'}$ 4.8, $J_{2',3'}$ 6.6, 2′-H), 5.23 (1 H, d, $J_{1',2'}$ 4.8, 1′-H), 7.21–7.51 (18 H, m, Ph and benzothiophene 3-, 5-, 6-H) and 7.70–7.81 (2 H, m, benzothiophene 4-, 7-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenyl-D-ribofuranosl)furan 4c. Foam, ν_{max}(neat)/cm^{-1} 1080, 1150, 1210 and 2800; HRMS (FAB, NBA) (Found: $C_{31}H_{30}O_5$, M = 482.2086; C, 77.5; H, 6.2. $C_{31}H_{30}O_5$ requires M = 482.2094; C, 77.2; H, 6.3%); δ_H(400 MHz; $CDCl_3$) δ_H(α-form) 1.33 (3 H, s, isopropylidene CH_3), 1.50 (3 H, s, isopropylidene CH_3), 3.21 (1 H, dd, $J_{4',5'a}$ 4.4, J_{gem} 10.5, 5′-H[a]), 3.35 (1 H, dd, $J_{4',5'b}$ 4.4, J_{gem} 10.5, 5′-H[b]), 4.34 (1 H, ddd, $J_{3',4'}$ 0.9, $J_{4',5'a}$ 4.4, $J_{4',5'b}$ 4.0, 4′-H), 4.77 (1 H, dd, $J_{2',3'}$ 6.0, $J_{3',4'}$ 0.9, 3′-H), 4.93 (1 H, dd, $J_{1',2'}$ 4.2, $J_{2',3'}$ 6.0, 2′-H), 5.31 (1 H, d, $J_{1',2'}$ 4.2, 1′-H), 6.39–6.52 (2 H, m, furan 3-, 4-H) and 7.21–7.47 (16 H, m, Ph and furan 5-H); δ_H(β-form) 1.35 (3 H, s, isopropylidene CH_3), 1.58 (3 H, s, isopropylidene CH_3), 3.22 (2 H, m, 5′-H), 4.34 (1 H, td, $J_{3',4'}$ 3.3, $J_{4',5'}$ 4.8, 4′-H), 4.69 (1 H, dd, $J_{2',3'}$ 6.3, $J_{3',4'}$ 3.3, 3′-H), 4.89 (1 H, dd, $J_{1',2'}$ 4.6, $J_{2',3'}$ 6.3, 2′-H), 4.96 (1 H, d, $J_{1',2'}$ 4.6, 1′-H), 6.30–6.33 (2 H, m, furan 3-, 4-H) and 7.20–7.47 (16 H, m, Ph and furan 5-H).

2-(2,3-*O*-Isopropylidene-5-*O*-triphenylmethyl-D-ribofuranosyl)indole 4d. Foam, ν_{max}(KBr)/cm^{-1} 705, 750, 860, 1075, 1100, 1200, 1365, 1375, 1420, 1440, 1485, 1585, 2900, 2950, 3025 and 3350; HRMS (FAB, NAB + H) (Found: $C_{35}H_{34}NO_4$, M + H = 532.2488. Calc. for $C_{35}H_{34}NO_4$: M + H = 532.2489) (Found: C, 78.9; H, 6.5; N, 2.4. $C_{35}H_{33}NO_4$ requires C, 79.1; H, 6.3; N, 2.6%); δ_H(500 MHz; $CDCl_3$) (β-form) 1.37 (3 H, s, isopropylidene CH_3), 1.61 (3 H, s, isopropylidene CH_3), 3.26 (1 H, dd, $J_{4',5'a}$ 4.5, J_{gem} 10.2, 5′-H[a]), 3.34 (1 H, dd, $J_{4',5'b}$ 3.9, J_{gem} 10.2, 5′-H[b]), 4.38 (1 H, m, 4′-H), 4.84 (1 H, dd, $J_{2',3'}$ 6.1, $J_{3',4'}$ 3.2, 3′-H), 4.88 (1 H, dd, $J_{1',2'}$ 3.3, $J_{2',3'}$ 6.1, 2′-H), 5.27 (1 H, d, $J_{1',2'}$ 3.3, 1′-H), 6.39 (1 H, m, indole 3-H), 6.65–7.53 (19 H, m, Ph and indole 4-, 5-, 6-, 7-H) and 8.69 (1 H, br s, indole 1-H).

2-D-Ribofuranosylthiophene 5a. Oil, HRMS (FAB, NBA + KI) (Found: $C_9H_{12}O_4SK$, M = 255.0105. Calc. for $C_9H_{12}O_4SK$: M = 255.0093); δ_H(400 MHz; $CDCl_3$–CD_3OD) (β-form) 3.75 (1 H, dd, $J_{4',5'a}$ 4.4, J_{gem} 12.1, 5′-H[a]), 3.83 (1 H, d, J_{gem} 12.1, 5′-H[b]), 4.02 (1 H, m, 4′-H), 4.06 (1 H, m, 2′-H), 4.13 (1 H, m, 3′-H), 5.04 (1 H, d, $J_{1',2'}$ 6.1, 1′-H), 7.01 (1 H, dd, $J_{3,4}$ 3.6, $J_{4,5}$ 5.0, thiophene 4-H), 7.10 (1 H, dd, $J_{3,4}$ 3.6, $J_{long\ range}$ 0.8, thiophene 3-H), 7.30 (1 H, d, $J_{4,5}$ 5.0, $J_{long\ range}$ 1.1 thiophene 5-H).

2-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)benzothiophene (5b-*O*-acetate). Oil, HRMS (FAB, NBA) (Found: $C_{19}H_{20}O_7S$, M = 392.0930. Calc. for $C_{19}H_{20}O_7S$: M = 392.0929); δ_H(400 MHz; $CDCl_3$) (β-form) 2.11–2.15 (9 H, m, Ac), 4.24–4.50 (3 H, m, 4′-H and 5′-H_2), 5.25–5.37 (3 H, m, 1′-, 2′-, 3′-H), 7.05–7.37 (3 H, m, benzothiophene 3-, 5-, 6-H) and 7.72–7.82 (2 H, m, benzothiophene 4-, 7-H).

2-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)furan (5c-*O*-acetate). Oil, HRMS (FAB, NBA + H) (Found: $C_{15}H_{19}O_8$, M + H = 327.1080. Calc. for $C_{15}H_{19}O_8$: M + H = 327.1080); δ_H(500 MHz; $CDCl_3$) (β-form) 2.03–2.12 (9 H, m, Ac), 2.89–3.03 (2 H, m, 5′-H_2), 4.13–5.50 (4 H, m, 1′-, 2′-, 3′-, 4′-H), 6.60–6.27 (1 H, m, furan 4-H), 6.35–6.39 (1 H, m, furan 3-H) and 7.26–7.31 (1 H, m, furan 5-H).

2-(D-Ribofuranosyl)indole 5d. Oil, HRMS (FAB, NBA + H) (Found: $C_{13}H_{16}NO_4$, M + H = 250.1072. Calc. for $C_{13}H_{16}NO_4$; M + H = 250.1079); δ_H(270 MHz; $CDCl_3$ + CD_3OD) (β-form) 3.27 (8 H, m, 2′-, 3′-, 4′-, 5′-H, 2′-, 3′-, 5′-OH), 5.00 (1 H, d, $J_{1',2'}$ 5.6, 1′-H), 6.45 (1 H, s, indole 3-H) and 7.03–7.57 (4 H, m, indole 4-, 5-, 6-, 7-H).

Preparation of 2-aryl-cadmium or -zinc 7a-, 7b-, 7e-, 7f-Cd or -Zn

All experiments were carried out under argon and Grignard reagents were prepared by the standard procedure: freshly prepared aryl Grignard reagent (THF solution 1.0 M; 2.0 mmol) was added dropwise to a suspension of well dried $CdCl_2$ or $ZnCl_2$ (1.0 mmol) in anhydrous THF (3 cm^3) at room temperature and the mixture was gently refluxed for 2–3 h.

2-Pyridylmagnesium bromide was prepared *via* the halogen–metal exchange reaction of 2-iodopyridine and ethylmagnesium bromide.[9] 2-Pyridyl-cadmium and -zinc were prepared as described above.

Preparation of 2-arylcerium chlorides 7a-, 7e-, 7f-Ce

Cerium chloride ($CeCl_3 \cdot H_2O$, 1.0 mmol) in the flask was heated in an oil-bath at 140 °C for 3 h.[10] After argon gas was introduced, the flask was cooled at 0 °C. Anhydrous THF was added and the solution was suspended under ultrasonic irradiation[11] for 1 h. Then aryllithium reagent (1.0 mmol) was added dropwise at −78 °C.

Preparation of 2-(*ribo*-pentitol-1-yl)-thiophene, -benzothiophene, -*N*-methylindole and -pyridine 8 using 2-aryl-cadmium or -zinc 7-Cd or -Zn

A solution of 2-aryl-cadmium or -zinc **7** (2.0 mmol) was added dropwise to a solution of 2,3,5-tri-*O*-benzyl-D-ribose (0.2 mmol) in dry THF (2 cm^3) at room temperature. Then, the solution was gently refluxed for 2–3 h. The mixture was quenched with water, neutralized with aqueous NH_4Cl, and extracted with Et_2O. The product was purified by PLC on silica gel [eluent: AcOEt–hexane (2 : 1)] to give products **8**.

Preparation of 2-(*ribo*-pentitol-1-yl)-thiophene, -*N*-methylindole and -pyridine 8 using 2-arylcerium chloride 7-Ce

To a solution of 2,3,5-tri-*O*-benzyl-D-ribose (0.2 mmol) in dry THF (2 cm^3) was added dropwise a solution of 2-arylcerium chloride **7** (2.0 mmol) at −78 °C. After being stirred for 10 min, the solution was gently warmed to −15 °C for 2 h. The mixture was quenched with water, neutralized with aqueous NH_4Cl,

and extracted with Et_2O. The product was purified by PLC on silica gel [eluent: AcOEt–hexane (2:1)] to give products **8**.

The stereochemistry of compound **8a** was determined by comparison with an authentic sample.[3]

***N*-Methyl-2-(2,3,5-tri-*O*-benzyl-D-*ribo*-pentitol-1-yl)indole 8e.** Oil, ν_{max}(neat)/cm^{-1} 730, 900, 1060, 1300, 1450, 1590, 1690, 2810, 2860, 2970 and 3350; HRMS (FAB, NBA) (Found: $C_{35}H_{37}NO_5$, M = 551.2676; C, 76.5; H, 6.6; N, 2.6. $C_{35}H_{37}NO_5$ requires M = 551.2672; C, 76.2; H, 6.8; N, 2.5%); δ_H(400 MHz; $CDCl_3$) (*R*-form) 2.68 (1 H, br s, 4′-OH), 3.34 (1 H, br s, 1′-OH), 3.50 (1 H, dd, $J_{4',5'a}$ 5.9, J_{gem} 9.7, 5′-H^a), 3.60 (1 H, dd, $J_{4',5'b}$ 2.9, J_{gem} 9.7, 5′-H^b), 3.63 (3 H, s, indole NCH_3), 3.67 (1 H, dd, $J_{2',3'}$ 2.9, $J_{3',4'}$ 7.7, 3′-H), 3.95 (1 H, m, 4′-H), 4.15 (1 H, dd, $J_{1',2'}$ 5.9, $J_{2',3'}$ 2.9, 2′-H), 4.39–4.78 (6 H, m, benzyl CH_2), 5.26 (1 H, d, $J_{1',2'}$ 5.9, 1′-H), 6.50 (1 H, s, indole 3-H) and 7.10 –7.63 (19 H, m, Ph and indole 4-, 5-, 6-, 7-H).

2-(2,3,5-Tri-*O*-benzyl-D-*ribo*-pentitol-1-yl)pyridine 8f. Oil, ν_{max}(neat)/cm^{-1} 700, 760, 1080, 1210, 1450, 1590, 2850, 3000 and 3400; HRMS (FAB, NBA + H) (Found: $C_{31}H_{34}NO_5$, M + H = 500.2435. Calc. for $C_{31}H_{34}NO_5$: M + H = 500.2437) (Found: C, 74.8; H, 6.9; N, 2.6. $C_{31}H_{33}NO_5$ requires C, 74.5; H, 6.7; N, 2.8%); δ_H(400 MHz; $CDCl_3$) (*R*-form) 3.62–3.76 (3 H, m, 5′-H_2 and 4′-OH), 3.88–4.20 (4 H, m, 2′-, 3′-, 4′-H and benzyl CH_2), 4.31 (1 H, br s, 1′-OH), 4.40–4.75 (5 H, m, benzyl CH_2), 5.12 (1 H, m, 1′-H), 7.03–7.70 (18 H, m, Ph and pyridine 3-, 4-, 5-H) and 8.50 (1 H, m, pyridine 6-H); δ_H(*S*-form) 3.33 (1 H, br s, 4′-OH), 3.58 (1 H, dd, $J_{4',5'a}$ 5.9, J_{gem} 9.7, 5′-H^a), 3.69 (1 H, dd, $J_{4',5'b}$ 1.8, J_{gem} 9.7, 5′-H^b), 4.03 (3 H, m, 2′-, 3′-, 4′-H), 4.29–4.62 (6 H, m, benzyl CH_2), 4.78 (1 H, br s, 1′-OH), 5.07 (1 H, d, $J_{1',2'}$ 7.0 1′-H), 7.09–7.65 (18, m, Ph and pyridine 3-, 4-, 5-H), 8.54 (1 H, d, $J_{5,6}$ 4.8 pyridine).

The stereochemistry of compounds **8e** and **8f** was determined as follows: the stereospecific cyclization of these compounds under Mitsunobu conditions gave the corresponding β-*C*-nucleosides [NOE: H-1′ ⟷ H-4].

Typical Mitsunobu conditions

A mixture of compound **8e** (53 mg, 0.095 mmol), triphenylphosphine (100 mg, 0.38 mmol), and dry THF (3 cm^3) was stirred for 15 min and then a THF solution of diethyl azodicarboxylate (DEAD) (60 mg, 0.03 mmol) was added dropwise to the mixture. After being stirred for 2.5 h, the reaction mixture was purified by column chromatography on silica gel [eluent: AcOEt–hexane (1:3)] to give *N*-methyl-2-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)indole.

2-[2-Deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentitol-1-yl]-*N*-methylindole 10e. Oil, ν_{max}(neat)/cm^{-1} 1060, 1460, 2825, 2900 and 3300; HRMS (FAB, NBA) (Found: $C_{26}H_{45}NO_5Si_2$, M = 507.2826; C, 61.8; H, 9.0; N, 2.7. $C_{26}H_{45}NO_5Si_2$ requires M = 507.2836; C, 61.5; H, 8.9; N, 2.8%); δ_H(400 MHz; $CDCl_3$) (*R*-form) 0.99–1.15 (28 H, m, TIPDS), 2.35–2.46 (3 H, m, 2′-H_2 and 1′- or 4′-OH), 3.53 (1 H, br s, 4′- or 1′-OH), 3.69 (1 H, m, 4′-H), 3.82 (3 H, s, indole NCH_3), 3.89 (1 H, d, $J_{4',5'a}$ 2.2, J_{gem} 11.7, 5′-H^a), 4.11–4.24 (2 H, m, 3′-H and 5′-H^b), 5.25 (1 H, d, $J_{1',2'}$ 8.4, 1′-H), 6.47 (1 H, s, indole 3-H), 7.07–7.21 (3 H, m, indole 5-, 6-, 7-H), and 7.56 (1 H, d, $J_{7,8}$ 7.7, indole 8-H); δ_H(*S*-form) 0.94–1.08 (28 H, m, TIPDS), 2.37–2.42 (2 H, m, 2′-H_2), 2.65 (2 H, br s, 1′-, 4′-OH), 3.72 (1 H, br d, $J_{4',5'b}$ 2.2, 4′-H), 3.78 (3 H, s, indole NCH_3), 3.85–4.07 (2 H, m, 3′-, 5′-H), 4.19 (1 H, d, $J_{4',5'b}$ 2.2, J_{gem} 11.7, 5′-H^b), 5.29 (1 H, m, 1′-H), 6.46 (1 H, s, indole 3-H), 7.10–7.28 (3 H, indole 5-, 6-, 7-H) and 7.55 (1 H, d, $J_{7,8}$ 7.7 indole 8-H).

After the stereospecific cyclization of *R*- and *S*-forms under Mitsunobu conditions, the stereochemistry of α- and β-anomers was established by NOESY data of NMR [H-1′ ⟷ H$^\beta$-2′ for α-anomer; H-1′ ⟷ H$^\alpha$-2′ for β-anomer]. The stereochemistry of compounds **10a**, **10b** and **10f** was determined according to our authentic samples.[8]

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