Coupling of ribofuranosyl fluoride and indoles

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The coupling reaction of a D-ribofuranosyl fluoride with indoles in the presence of boron trifluoride gives the corresponding *C*-nucleosides in a stereoselective manner depending upon reaction temperatures and solvents: the β-anomer is preferred under such conditions as −15 to −40 °C in nitroethane while the α-anomer is preferred at −78 °C in propiononitrile.

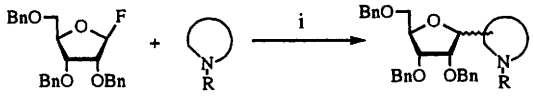
Introduction

Our study directed toward *C*-nucleoside synthesis[1] has stimulated renewed interest in their straightward synthesis. In the synthesis of *C*-nucleosides, D-ribofuranosyl bromides or chlorides have been used as a general sugar donor. However, many careful treatments are required for them to undergo a clean reaction, due to their instability to moisture. On the other hand, D-ribofuranosyl fluorides are moisture-stable sugar donors and, therefore, one was chosen as a good candidate for the present study.

D-Glucopyranosyl fluorides have been utilized for the general glucosylation reaction in organic synthesis.[2] We found that tri-*O*-benzyl-D-ribofuranosyl fluoride could be coupled to indoles easily. This reaction shows that the electrophilic aromatic substitutions are performed on indoles. To our knowledge, the use of D-ribofuranosyl fluorides is rare in the synthesis of *C*-nucleosides. Therefore, we report herein this method as a simple and useful synthesis for *C*-nucleosides.

Results and discussion

The coupling reaction was carried out as following (Scheme 1).



1 **2** **3**

Scheme 1 Coupling reaction of fluoride **1** with amines **2**. *Reagent:* i, BF_3·OEt_2, solvent.

A solution of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride **1** in dry organic solvents such as CH_2Cl_2, EtCN and $EtNO_2$ was allowed to react with indoles **2** in the presence of BF_3·OEt_2 at −78 to 0 °C. Although several Lewis acids such as $SnCl_2$, $SnCl_4$, $TiCl_4$, $Yb(OTf)_3$, trimethylsilyl trifluoromethanesulfonate (TMSOTf) and BF_3·OEt_2 were examined in the present reaction, the use of BF_3·OEt_2 gave the best results from preliminary experiments, and was therefore used in the present reactions. The preparation of compound **3** is summarized in Table 1.

In the case of 2-ethoxycarbonylindole **2b**, its NH group didn't require the protection, owing to the intramolecular hydrogen bond with the carbonyl group at the 2-position. In a comparison of runs 9 and 10, the yield decreased in run 10, perhaps because the hydrogen bond weakens at higher temperature, a suggestion which is supported by the variable-temperature NMR data shown in Table 2.

1-Phenylsulfonyl-7-azaindole was allowed to react with fluoride **1** to give the corresponding product **3** in 45% yield, while the use of 1-(*tert*-butyldimethylsilyl)-7-azaindole **2e** increased the yield of the corresponding product **3** (runs 18 and 19). Although 1-phenylsulfonylpyrazole didn't undergo this reaction at all, 1-benzyl-5-(trimethylsilyl)pyrazole **2g** underwent this reaction in CH_2Cl_2 to give product **3g** in 7% yield.

Solvent effect on stereoselectivity

In preliminary tests the reaction of fluoride **1** and phenylsulfonylindole **2a** was performed in such organic solvents as CH_2Cl_2, EtCN and $EtNO_2$. As a general tendency for the stereoselectivity of this reaction, α-selectivity increased according to the following order: EtCN > $EtNO_2$ > CH_2Cl_2 (runs 1, 3 and 7 in Table 1). In order to obtain the α-anomer of product **3a** exclusively, the use of CH_2Cl_2–EtCN (2.5%) solution at −78 °C gave the best result (use of EtCN alone gave exclusively the α-anomer, but only in 8% yield). This same tendency was also recognized in the reactions of indoles **2b** and **2f**. Therefore, indoles **2c** and **2e** was allowed to react in both EtCN and $EtNO_2$.

The predominance of the α-anomer product in the propiononitrile reaction may be attributable to its strong affinity for an intermediary oxocarbenium ion generated in this reaction.[3]

Temperature effect on stereoselectivity

As a general tendency of reaction temperature, high temperatures gave β-selectivity while low temperatures gave α-selectivity (runs 1 and 2; runs 7 and 8). An especially marked tendency of the reaction temperature was observed in the use of $EtNO_2$. The result is shown in Table 3 and Fig. 1.

Epimerization of product **3a** was then examined in $EtNO_2$ at −15 °C using BF_3·OEt_2. After treatment for 0.5 h, an α,β-mixture (91:9) of **3a** changed to a 9:91 mixture. The ratio 9:91 is the equilibrium ratio between α and β anomers at −15 °C. Therefore, the ΔG value at this temperature is estimated as 1.2 kcal mol^{-1}.† The epimerization is considered to take place as shown in Scheme 2.

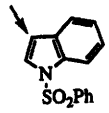
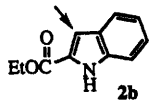
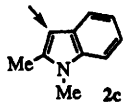
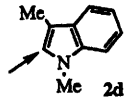
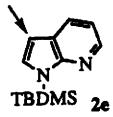
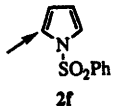
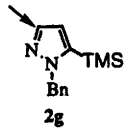
Judging from the above result, the α-anomer of compound **3a** is a kinetically controlled product and its β-anomer is a thermodynamically controlled product. This fact is supported by the heats of formation for the α and β anomers of **3a**, which were calculated by PM3 (MOL-MOLIS™ version 2.2RO MOPAC version 6.10, Stewart): ΔH_f = −46.6 kcal mol^{-1} for α-anomer and −49.7 kcal mol^{-1} for β-anomer. Therefore, the β-anomers of products **3** could be obtained exclusively on treatment of compounds **3** with CF_3CO_2H (TFA) (Table 4).[1d]

Structure determination

The α- and β-anomers of products **3** were determined by their coupling constants ($J_{1',2'}$-values) and nuclear Overhauser enhancement (NOE) data from ^1H NMR spectroscopy (Table

† 1 cal = 4.184 J.

Table 1 Preparation of compound 3

Indoles 2	Run	Solvent	Temp. (T/°C)	Time (t/h)	Yield (%)	α/β
 2a	1	CH_2Cl_2	−78	1.0	88	50/50
	2	CH_2Cl_2	−15	0.5	96	11/89
	3	EtCN	−78	1.0	8	α
	4	EtCN	0	1.0	23	80/20
	5	CH_2Cl_2–EtCN (0.5%)	−78	1.0	82	80/20
	6	CH_2Cl_2–EtCN (2.5%)	−78	1.0	72	91/9
	7	$EtNO_2$	−78	1.0	79	84/16
	8	$EtNO_2$	−40	0.5	99	9/91
 2b	9	CH_2Cl_2	−78	1.0	41	21/79
	10	CH_2Cl_2	−15	0.5	24	25/75
	11	EtCN	−78	1.0	7	α
	12	$EtNO_2$	−40	1.0	36	32/68
 2c	13	EtCN	−78	1.0	13	β
	14	$EtNO_2$	−15	0.5	48	β
 2d	15	CH_2Cl_2	−78	1.0	31	80/20
	16	EtCN	−78	1.0	20	50/50
	17	$EtNO_2$	−15	0.5	13	28/72
 2e	18	EtCN	−78	1.0	62 (92)[a]	74/26
	19	$EtNO_2$	−15	0.5	80	18/82
 2f	20	CH_2Cl_2	−78	1.0	80	19/81
	21	EtCN	−78	1.0	39	α
	22	$EtNO_2$	−40	0.5	83	15/85
 2g	23	CH_2Cl_2	−78	1.0	7	α

→: C–C bond-forming position. [a] Conversion yield.

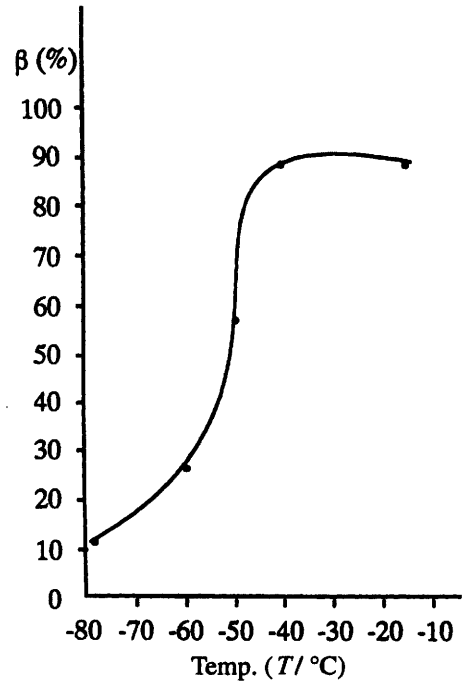
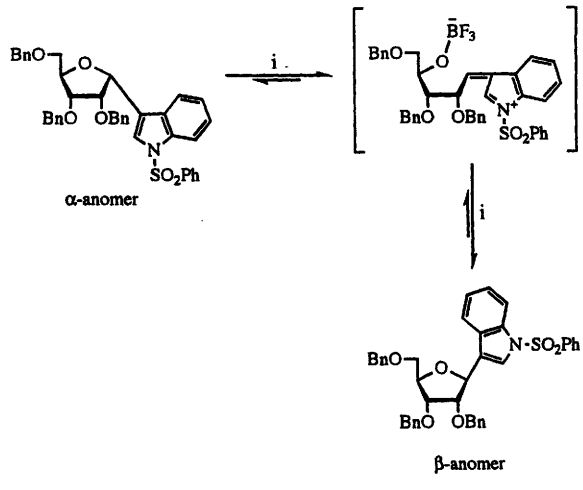


Fig. 1 Reaction temperature dependence of β-selectivity



Scheme 2 Epimerization of compound **3a**. *Reagent:* i, BF_3.

5). Although the coupling constants for both anomers of compound **3f** are very similar, the α-anomer lacks an NOE between 1′-H and 4′-H.

Deprotection

The phenylsulfonyl group of compounds **3** (**3a** and **3f**) could be removed easily with potassium hydroxide in 1,4-dioxane

Table 2 Chemical shifts of NH at several temperatures

Temp. (T/°C)	NH (ppm)
25	9.05
15	9.11
0	9.23
−15	9.37
−25	9.48
−35	9.60
−45	9.75
−55	9.94

Table 3 Yield and stereoselectivity of compound **3a** at several temperatures[a]

Run	Temp. (T/°C)	Yield (%)	α/β
1	−15	94	9/91
2	−40	99	9/91
3	−50	93	41/59
4	−60	96	71/29
5	−78	74	86/14

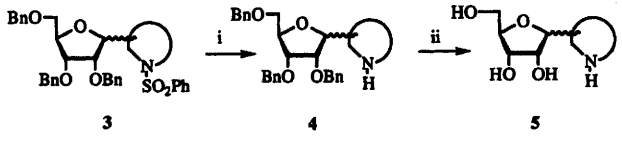
[a] Reaction conditions: $EtNO_2$, BF_3·OEt_2, 0.5 h.

Table 4 Epimerization of compounds **3**

Run	3	α/β[a]
1	**3a**	59/41→12/88
2	**3b**	32/68→25/75
3	**3e**[b]	74/26→49/51
4	**3f**	α→22/78

[a] The ratios after treatment with TFA for 1 day at room temperature. [b] Desilylated product.

solution containing 18-crown-6[4] to afford products **4** (Scheme 3). Debenzylation of compound **4a** was carried out in the usual way using boron trichloride[5] to give compound **5a**. The α and β anomers of compound **5a** could be separated by recycling preparative HPLC.



3 4 5

Scheme 3 Deprotection of **3**. *Reagents:* i, KOH, 18-crown-6; ii, BCl_3.

Experimental

Microanalyses were performed with a Perkin-Elmer 2400 elemental analyser at the Chemical Analysis Center of Chiba University. IR spectra were recorded on a Hitachi 215 spectrometer. Mass spectra were obtained on Hitachi M-60 and JEOL JMS-HX110 mass spectrometers. ^1H and ^{13}C NMR spectra were measured [$CDCl_3$ as solvent (unless specified otherwise), using tetramethylsilane (TMS) as internal reference] with JEOL JNM-FX-270 and JNM-GSX-500 spectrometers. Chemical shifts are expressed in δ values; J values are given in Hz. 2D ^1H NMR (COSY and NOESY) data were measured with the JNM-GSX-500 spectrometer. Wakogel C-200 and C-300 was used for TLC, and Wakogel B-5F for preparative TLC (PLC). Recycling preparative HPLC was performed with a Japan Analytical Industry LC-908 instrument.

Materials

2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl fluoride **1**,[6] 1-(phenylsulfonyl)indole **2a**,[7] and 1-(phenylsulfonyl)pyrrole **2f**[7] were prepared according to the literature.

Synthesis of *C*-nucleosides 3; typical procedure

To a solution of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride **1** (50 mg, 0.12 mmol) and each aromatic heterocycle **2** (0.36 mmol) in dry CH_2Cl_2 (2 ml) was added BF_3·OEt_2 (0.1 ml, 0.84 mmol) at −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was treated with aq. $NaHCO_3$ (6 ml), extracted with $CHCl_3$, and the extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified in the usual way using PLC on silica gel.

1-(*tert*-Butyldimethylsilyl)-7-azaindole 2e

To a solution of 7-azaindole (500 mg, 4.2 mmol) in dry THF (10 ml) was added BuLi (hexane solution; 5 mmol) dropwise and the mixture was stirred for 0.5 h at room temperature. To the resultant mixture was added *tert*-butyldimethysilyl chloride (770 mg) and the mixture was stirred for 1 day at room temperature before being treated with aq. NH_4Cl (10 ml), extracted with $CHCl_3$, and the extract dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography [eluent: hexane–ethyl acetate (4:1), R_f 0.8] (94%), oil, ν_{max}(neat)/cm^{-1} 2900, 1400, 1280, 1160 and 790; δ_H(270 MHz) 0.63 (6 H, s, Me), 0.93 (9 H, s, Bu^t), 6.52 (1 H, d, $J_{2,3}$ 3.6, 3-H), 6.99–7.04 (1 H, m, 5-H), 7.23 (1 H, d, $J_{2,3}$ 3.6, 2-H), 7.85 (1 H, dd, $J_{4,5}$ 7.9, $J_{4,6}$ 1.7, 4-H) and 8.26 (1 H, dd, $J_{5,6}$ 4.6, $J_{4,6}$ 1.7, 6-H).

The following *C*-nucleorides were prepared.

1-Phenylsulfonyl-3-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)indole 3a. Oil, ν_{max}(neat)/cm^{-1} 2820, 1440, 1360, 1170 and 730 [HRMS (FAB) Found: M^+, 659.2271. Calc. for $C_{40}H_{37}NO_6S$: M, 659.2342]; δ_H(500 MHz) (α-anomer) 3.61 (1 H, dd, J_{gem} 10.7, $J_{4',5'}$ 3.3, 5'-H), 3.76 (1 H, dd, J_{gem} 10.7, $J_{4',5'}$ 2.8, 5'-H), 4.12–4.17 (2 H, m, 2'- and 3'-H), 4.28–4.62 (7 H, m, 4'-H and PhCH_2), 5.27 (1 H, d, $J_{1',2'}$ 3.3, 1'-H), 6.87 (J 7.4, 2 H, d) and 7.04–8.01 (23 H, m, indole 2-, 4-, 5-, 6- and 7-H, SO_2Ph and Ph).

δ_H(β-Anomer) 3.60 (1 H, dd, J_{gem} 10.5, $J_{4',5'}$ 3.6, 5'-H), 3.70 (1 H, dd, J_{gem} 10.5, $J_{4',5'}$ 3.6, 5'-H), 4.03 (1 H, dd, $J_{1',2'}$ 6.6, $J_{2',3'}$ 5.2, 2'-H), 4.08 (1 H, dd, $J_{2',3'}$ 5.2, $J_{3',4'}$ 4.1, 3'-H), 4.30–4.66 (7 H, m, 4'-H and PhCH_2), 5.19 (1 H, d, $J_{1',2'}$ 6.6, 1'-H) and 7.01–7.99 (25 H, m, indole 2-, 4-, 5-, 6- and 7-H, SO_2Ph and Ph); δ_C(125 MHz) 70.1 (C-5'), 72.2, 72.4 and 73.5 (benzyl CH_2), 77.1 (C-3'), 77.4 (C-2'), 81.2 (C-4'), 81.8 (C-1'), 113.5 (indole C-6 and -7), 120.9 (indole C-4), 121.8 (indole C-3), 123.2 (indole C-5), 124.1 (indole C-2), 124.7–128.4 (Ph), 128.7 (indole C-9), 129.2–133.7 (Ph), 135.5 (indole C-8) and 137.5–138.1 (Ph).

2-Ethoxycarbonyl-3-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)indole 3b. Oil, ν_{max}(neat)/cm^{-1} 3270, 2820, 1690, 1240, 1100 and 740 [HRMS (FAB) Found: $(M + H)^+$, 592.2690. Calc. for $C_{37}H_{38}NO_6$: $(M + H)$, 592.2699]; δ_H(500 MHz) (α-anomer) 1.35 (3 H, t, J 7.3, CH_3CH_2O), 3.68–3.86 (2 H, m, 5'-H_2), 4.28–4.65 (11 H, m, 2'-, 3'- and 4'-H, CH_3CH_2O and PhCH_2O), 6.02 (1 H, d, $J_{1',2'}$ 2.8, 1'-H), 6.71 (2 H, d, J 6.9, Ph), 7.04–7.33 (16 H, m, indole 5-, 6- and 7-H, and Ph), 8.17 (1 H, d, $J_{4,5}$ 8.3, indole 4-H) and 8.76 (1 H, br s, indole 1-H).

δ_H(β-Anomer) 1.36 (3 H, t, J 7.2, CH_3CH_2O), 3.72–3.86 (2 H, m, 5'-H_2), 4.27–4.79 (11 H, m, 2'-, 3'- and 4'-H, CH_3CH_2O and PhCH_2), 6.05 (1 H, d, $J_{1',2'}$ 6.3, 1'-H), 6.85–6.88 (1 H, m, indole 5-H), 7.06–7.36 (17 H, m, indole 6- and 7-H and Ph), 7.92 (1 H, d, $J_{4,5}$ 8.0, indole 4-H) and 8.89 (1 H, br s, indole 1-H).

1,2-Dimethyl-3-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)indole 3c. Oil, ν_{max}(neat)/cm^{-1} 2850, 1440, 1360, 1130 and 740 [HRMS (FAB) Found: M^+, 547.2724. Calc. for $C_{36}H_{37}NO_4$: M, 547.2723]; δ_H(500 MHz) (β-anomer) 2.39 (3 H, s, 2-CH_3), 3.63 (3 H, s, 1-CH_3), 3.66 (1 H, dd, J_{gem} 10.2, $J_{4',5'}$ 3.9, 5'-H), 3.72 (1 H, dd, J_{gem} 10.2, $J_{4',5'}$ 3.9, 5'-H), 4.11–4.15 (1 H, m, 3'-H), 4.26 (1 H, dd, $J_{3',4'}$ 7.7, $J_{4',5'}$ 3.9, 4'-H), 4.31 (1 H, dd, $J_{1',2'}$ 8.0, $J_{2',3'}$ 6.3, 2'-H), 4.36 (2 H, s, PhCH_2), 4.53–4.75 (4 H, m, PhCH_2), 5.21 (1 H, d, $J_{1',2'}$ 8.0, 1'-H), 6.89 (1 H, t, $J_{4,5}$ = $J_{5,6}$ = 8.0, indole 5-H), 7.03–7.37 (17 H, m, indole 6- and

Table 5 $J_{1',2'}$-values and NOE data of compound **3**

	α-Anomer		β-Anomer		
		NOE (%)		NOE (%)	
3	$J_{1',2'}$ (Hz)	1'-H ⇌ 2'-H	$J_{1',2'}$ (Hz)	1'-H ⇌ 2'-H	1'-H ⇌ 4'-H
3a	3.3	7.1	6.6	1.6	2.0
3b	2.8	9.6	6.3	N.O.[a]	8.6
3c			8.0	N.O.[a]	8.7
3d	3.0	8.9	8.0	N.O.[a]	3.2
3e	3.3	5.9	6.9	3.4	3.8
3f	2.8	4.1	3.3	3.5	3.7

[a] N.O.: not observed.

7-H, and Ph) and 7.64 (1 H, d, indole 4-H, $J_{4,5}$ 8.0, indole 4-H).

1,3-Dimethyl-2-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)indole 3d. Oil, ν_{max}(neat)/cm^{-1} 2830, 1440, 1360, 1130 and 740 [HRMS (FAB) Found: M$^+$, 547.2724]; δ_H(500 MHz) (α-anomer) 2.27 (3 H, s, 3-CH_3), 3.66–3.81 (2 H, m, 5'-H_2), 3.82 (3 H, s, 1-CH_3), 3.97 (1 H, d, *J* 11.8), 4.06–4.64 (8 H, m, 2'-, 3'- and 4'-H, and PhCH_2), 5.48 (d, 1 H, $J_{1',2'}$ 3.0, 1'-H), 6.89 (2 H, d, *J* 7.2), 7.08–7.37 (16 H, m, indole 5-, 6- and 7-H, and Ph) and 7.54 (1 H, d, $J_{4,5}$ 7.7, indole 4-H).

δ_H(β-Anomer) 2.36 (3 H, s, 3-CH_3), 3.59 (3 H, s, 1-CH_3), 3.61–3.70 (3 H, m, 4'-H and 5'-H_2), 4.10–4.79 (8 H, m, 2'- and 3'-H, PhCH_2), 5.32 (1 H, d, $J_{1',2'}$ 8.0, 1'-H), 6.98 (2 H, d, *J* 7.2), 7.08–7.37 (16 H, m, indole 5-, 6- and 7-H, and Ph) and 7.54 (1 H, d, $J_{4,5}$ 7.7, indole 4-H).

1-(*tert*-Butyldimethylsilyl)-3-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-7-azaindole 3e. Oil, ν_{max}(neat)/cm^{-1} 2900, 1440, 1290, 1140 and 750 [HRMS (FAB) Found: (M + H)$^+$, 635.3309. Calc. for $C_{39}H_{47}N_2O_4Si$: (*M* + H), 635.3305]; δ_H(500 MHz) (α-anomer) 0.57 and 0.58 (3 H × 2, s × 2, Me), 0.91 (9 H, s, Bu^t), 3.61–3.77 (2 H, m, 5'-H_2), 4.10–4.68 (9 H, m, 2'-, 3'- and 4'-H, and PhCH_2), 5.33 (1 H, d, $J_{1',2'}$ 3.3, 1'-H), 6.97 (1 H, dd, $J_{4,5}$ 7.9, $J_{5,6}$ 4.6, indole 5-H), 7.10–7.35 (16 H, m, indole 2-H and Ph), 7.97 (1 H, dd, $J_{4,5}$ 7.9, $J_{4,6}$ 1.6, indole 4-H) and 8.24 (1 H, dd, $J_{4,6}$ 1.6, $J_{5,6}$ 4.6, indole 6-H).

δ_H(β-Anomer) 0.58 (3 H × 2, s × 2, Me), 0.91 (9 H, s, Bu^t), 3.62 (1 H, dd, J_{gem} 10.4, $J_{4',5'}$ 3.6, 5'-H), 3.72 (1 H, dd, J_{gem} 10.4, $J_{4',5'}$ 3.9, 5'-H), 4.10–4.14 (2 H, m, 2'- and 3'-H), 4.32 (1 H, dd, $J_{3',4'}$ 6.9, $J_{4',5'}$ 3.6 (4'-H), 4.43, 4.49, 4.55, 4.60, 4.63 and 4.70 (1 H × 6, d × 6, benzyl-H, J_{gem} 12.1 PhCH_2), 5.21 (1 H, d, $J_{1',2'}$ 6.9 1'-H), 6.80 (1 H , dd, $J_{4,5}$ 8.0, $J_{5,6}$ 4.7, indole 5-H), 7.08–7.36 (16 H, m, indole 2-H and Ph), 7.86 (1 H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 1.7, indole 4-H) and 8.21 (1 H, dd, $J_{4,6}$ 1.7, $J_{5,6}$ 4.7, indole 6-H); δ_C(125 MHz) −4.3, 18.9 and 26.5 (TBDMS), 70.5 (C-5'), 72.0, 72.2 and 73.5 (benzyl CH_2), 77.5 (C-3'), 77.8 (C-2'), 81.1 (C-4'), 81.8 (C-1'), 114.8 (indole C-3), 115.6 (indole C-5), 120.5 (indole C-9), 127.6 (indole C-2), 127.6–128.4 (Ph), 129.4 (indole C-4), 137.8 and 138.1 (Ph), 142.5 (indole C-6) and 154.6 (indole C-8).

1-Phenylsulfonyl-2-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)pyrrole 3f. Oil, ν_{max}(neat)/cm^{-1} 2870, 1740, 1360, 1150 and 740 [HRMS (FAB) Found: (M + H)$^+$, 610.2263. Calc. for $C_{36}H_{36}NO_6S$: (*M* + H), 610.2263]; δ_H(500 MHz) (α-anomer) 3.56–4.71 (2'-, m, 11 H, 3'- and 4'-H, 5'-H_2, and PhCH_2), 5.39 (1 H, d, $J_{1',2'}$ 2.8 1'-H), 6.33 (1 H, dd, $J_{3,4}$ 3.2, $J_{4,5}$ 3.2 pyrrole 4-H), 6.59–6.61 (1 H, m, pyrrole 3-H) and 7.13–7.70 (21 H, m, pyrrole 5-H, SO_2Ph and Ph).

δ_H(β-Anomer) 3.56 (1 H, dd, J_{gem} 7.3, $J_{4',5'}$ 3.9, 5'-H), 3.57 (1 H, dd, J_{gem} 7.3, $J_{4',5'}$ 3.0, 5'-H), 4.08–4.27 (3 H, m, 2'-, 3'- and 4'-H), 4.41–4.71 (6 H, m, PhCH_2), 5.42 (1 H, d, $J_{1',2'}$ 3.3, 1'-H), 6.16 (1 H, dd, $J_{3,4}$ = $J_{4,5}$ = 3.4, pyrrole 4-H, 1 H, dd), 6.42–6.44 (1 H, m, pyrrole 3-H), 7.17–7.33 (16 H, m, pyrrole 5-H and Ph), 7.36–7.41 (3 H, m, SO_2Ph *m*, *p*-H) and 7.80 (2 H, dd, J_1 1.0, J_2 7.3, SO_2Ph *o*-H); δ_C(125 MHz) 69.2 (C-5'), 72.3, 73.3 (benzyl CH_2), 76.9 (C-3'), 77.4 (C-2'), 79.8 (C-4'), 80.8 (C-1'), 112.0–123.6 (pyrrole C-3, -4 and -5), 126.9–129.3 (Ph), 134.0 (pyrrole C-2) and 137.9–139.1 (Ph).

1-Benzyl-3-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-5-(trimethylsilyl)pyrazole 3g. Oil, ν_{max}(neat)/cm^{-1} 2900, 1420, 1100 and 700; δ_H(270 MHz) (α-anomer) 0.07, 0.09 and 0.20 (3 H × 3, s × 3, $SiMe_3$), 3.54–3.72 (2 H, m, 5'-H), 4.01–4.60 (9 H, m, 2'-, 3'- and 4'-H and PhCH_2O), 5.09 (1 H, d, $J_{1',2'}$ 3.9, 1'-H), 5.45 (2 H, s, NCH_2Ph), 6.44 (1 H, d, *J* 1.6, 4-H) and 6.91–7.59 (20 H, m, Ph).

Deprotection

3-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)indole 4a. A mixture of compound **3a** (131.8 mg, 0.2 mmol), 18-crown-6 (52.8 mg, 0.2 mmol), KOH (1.0 g, 17.9 mmol), methanol (2 ml) and 1,4-dioxane (2 ml) was stirred for 1 h at room temperature. The resulting mixture was treated with 1 M HCl (15 ml), extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by PLC on silica gel [developer hexane–ethyl acetate (4:1); R_f 0.3] (81%), oil, ν_{max}(neat)/cm^{-1} 3250, 2800, 1420 and 1060 [HRMS (FAB) Found: M$^+$, 519.2388; C, 78.9; H, 6.4; N, 3.0% Calc. for $C_{34}H_{33}NO_4$: *M*, 519.2410, C, 78.59; H, 6.40; N, 2.70%]; δ_H(500 MHz) (α-anomer) 3.64–4.69 (11 H, m, 2'-, 3'- and 4'-H, 5'-H_2 and PhCH_2), 5.45 (1 H, d, $J_{1',2'}$ 3.4, 1'-H), 6.97–7.65 (20 H, m, indole 2-, 4-, 5-, 6- and 7-H, and Ph) and 8.16 (1 H, br s, indole 1-H).

δ_H(β-Anomer) 3.66 (1 H, dd, J_{gem} 10.5, $J_{4',5'}$ 3.6, 5'-H), 3.75 (1 H, dd, J_{gem} 10.5, $J_{4',5'}$ 3.9), 4.11–4.35 (3 H, m, 2'-, 3'- and 4'-H), 4.53–4.69 (6 H, m, PhCH_2), 5.33 (1 H, d, $J_{1',2'}$ 6.3, 1'-H, 5'-H), 6.99 (1 H, dd, $J_{4,5}$ 8.0, $J_{5,6}$ 0.8 indole 5-H), 7.15–7.36 (18 H, m, indole 2-, 6- and 7-H and Ph), 7.65 (1 H, d, $J_{4,5}$ 8.0, indole 4-H) and 8.02 (1 H, br s, indole 1-H).

2-(2,3,5-Tri-*O*-benzyl-D-ribofuranosyl)pyrrole 4f. Desulfonylation of compound **3f** was carried out by the same method as described for its analogue **3a**. Compound **4f** was obtained as an oil, ν_{max}(neat)/cm^{-1} 3260, 2840, 1440, 1100 [HRMS (FAB) Found: (M + H)$^+$, 470.2336. Calc. for $C_{30}H_{32}NO_4$: (*M* + H), 470.2331] (Found: C, 76.6; H, 6.6; N, 3.2. Calc. for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98%); δ_H(500 MHz) (α-anomer) 3.69 (1 H, dd, J_{gem} 10.2, $J_{4',5'}$ 1.7, 5'-H), 3.98 (1 H, dd, J_{gem} 10.2, $J_{4',5'}$ 2.1, 5'-H), 3.93–4.76 (9 H, m, 2'-, 3'- and 4'-H, and PhCH_2), 5.22 (1 H, d, $J_{1',2'}$ 2.0, 1'-H), 5.89–6.05 (3 H, m, pyrrole 3-, 4- and 5-H), 7.15–7.38 (15 H, m, Ph) and 9.42 (1 H, br s, pyrrole 1-H).

δ_H(β-Anomer) 3.51 (1 H, dd, J_{gem} 10.1, $J_{4',5'}$ 3.3, 5'-H), 3.60 (1 H, dd, J_{gem} 10.1, $J_{4',5'}$ 3.4, 5'-H), 3.93–4.76 (9 H, m, 2'-, 3'- and 4'-H, and PhCH_2), 5.18 (1 H, d, $J_{1',2'}$ 4.6 1'-H), 6.05–6.19 (3 H, m, pyrrole 3-, 4- and 5-H), 7.15–7.38 (15 H, m, Ph) and 9.29 (1 H, br s, pyrrole 1-H).

3-(D-Ribofuranosyl)indole 5a. To a solution of compound **4a** (88.2 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 being stirred 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 powdered $NaHCO_3$ at room temperature. The resulting mixture was filtered, and washed with dry methanol. The combined filtrate and washings were condensed, and purified by PLC on silica gel [developer $CHCl_3$–MeOH (9:1); R_f 0.2] (42%); δ_H(270 MHz; $CDCl_3$–CD_3OD) (α-anomer) 3.25–4.28 (8 H, m, 2′-, 3′- and 4′-H, 5′-H_2 and 2′-, 3′-, and 5′-OH), 5.05 (1 H, d, $J_{1',2'}$ 6.0, 1′-H), 7.05–7.37 (4 H, m, indole 2-, 5-, 6- and 7-H), 7.68 (1 H, d, $J_{4,5}$ 7.7, indole 4-H) and 9.46 (1 H, br s, indole 1-H).

δ_H(β-Anomer) 3.25–4.28 (8 H, m, 2′-, 3′- and 4′-H, 5′-H_2, and 2′-, 3′- and 5′-OH), 4.80 (1 H, d, $J_{1',2'}$ 9, 1′-H), 7.05–7.37 (4 H, m, indole 2-, 5-, 6- and 7-H), 7.61 (1 H, d, $J_{4,5}$ 8.0, indole 4-H) and 9.54 (1 H, br s, indole 1-H). Each anomer was separated from a mixture of α- and β-anomers by HPLC [column: JAIGEL GS-320 (20 mm φ × 500 mm); eluent: MeOH; cycle: 12 times].

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References

1 (*a*) H. Togo, M. Aoki and M. Yokoyama, *Tetrahedron Lett.*, 1991, **32**, 6559; (*b*) H. Togo, S. Ishigami and M. Yokoyama, *Chem. Lett.*, 1992, 1673; (*c*) H. Togo, M. Aoki, T. Kuramochi and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2417; (*d*) M. Yokoyama, T. Tanabe, A. Toyoshima and H. Togo, *Synthesis*, 1993, 517; (*e*) M. Yokoyama, A. Toyoshima, T. Akiba and H. Togo, *Chem. Lett.*, 1994, 265; S. Ishigami, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2407; H. Togo, S. Ishigami, M. Fujii, T. Ikuma and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2931; M. Yokoyama, T. Akiba and H. Togo, *Synthesis*, 1995, 638; M. Yokoyama, M. Nomura, T. Tanabe and H. Togo, *Heteroatom Chem.*, 1995, **6**, 189.

2 T. Mukaiyama, Y. Murai and S. Shoda, *Chem. Lett.*, 1981, 431; S. Hashimoto, M. Hayashi and R. Noyori, *Tetrahedron Lett.*, 1984, **25**, 1379; T. Matsumoto, M. Katsuki, H. Jona and K. Suzuki, *J. Am. Chem. Soc.*, 1991, **113**, 6982; M. Chemielewski, J. N. BeMiller and D. P. Cerretti, *Carbohydr. Res.*, 1981, **97**, C1; G. Grynkiewicz and J. N. BeMiller, *Carbohydr. Res.*, 1982, **108**, 229; K. C. Nicolaou, R. E. Dolle, A. Chucholowski and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, 1984, 1153; K. C. Nicolaou, A. Chucholowski, R. E. Dolle and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, 1984, 1155; R. B. Myers and Y. C. Lee, *Carbohydr. Res.*, 1984, **132**, 61; Y. Araki, N. Kobayashi and Y. Ishido *Carbohydr. Res.*, 1987, **171**, 125; T. Matsumoto, M. Katsuki and K. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 833; K. N. Drew and P. H. Gross, *J. Org. Chem.*, 1991, **56**, 509; D. E. Levy and C. Tang, *The Chemistry of C-Glycosides*, Tetrahedron Organic Series, Pergamon Elsevier, New York, 1995, vol. 13, pp. 178, 184, 185.

3 R. R. Schmidt, M. Behrendt and A. Toepfer, *Synlett*, 1990, 694.

4 J. Rokach, P. Hamel, M. Kakushima and G. M. Smith, *Tetrahedron Lett.*, 1981, **22**, 4901.

5 L. Hsu, D. S. Wise, L. S. Kucera, J. C. Drach and L. B. Townsend, *J. Org. Chem.*, 1992, **57**, 3354.

6 G. H. Posner and S. R. Haines, *Tetrahedron Lett.*, 1985, **26**, 5; T. Mukaiyama, Y. Hashimoto and S. Shoda, *Chem. Lett.*, 1983, 935.

7 E. P. Papadopoulos and N. F. Haidar, *Tetrahedron Lett.*, 1968, 1721.

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