Coupling of ribofuranosyl fluoride and indoles

Masataka Yokoyama,*[a,b] Mitsuru Nomura,[a] Hideo Togo[a] and Hiroko Seki[b]

[a] Department of Chemistry, Faculty of Science and [b] Chemical Analysis Center, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263, Japan

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.

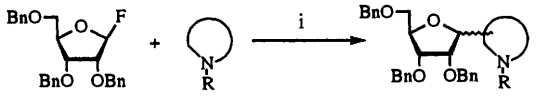
Introduction

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.

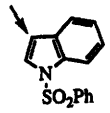
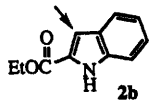
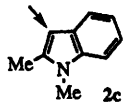
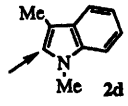
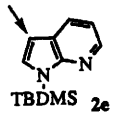
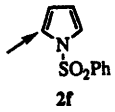
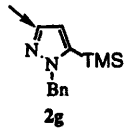
Judging from the above result, the α-anomer of compound **3a** is a kinetically controlled product and its β-anomer is a thermodynamically controlled product. This fact is supported by the heats of formation for the α and β anomers of **3a**, which were calculated by PM3 (MOL-MOLIS™ version 2.2RO MOPAC 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.

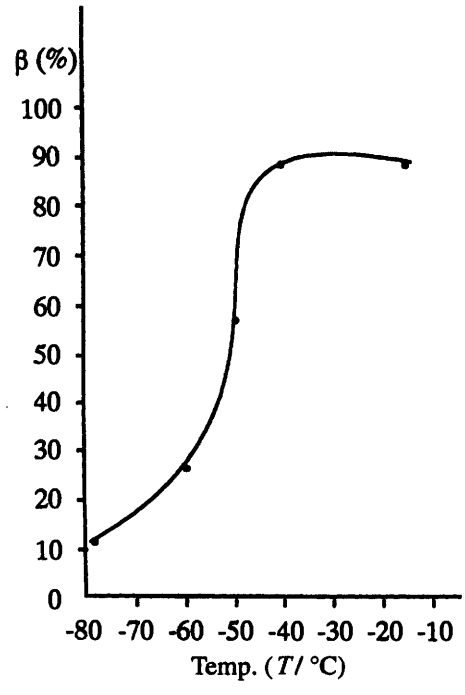
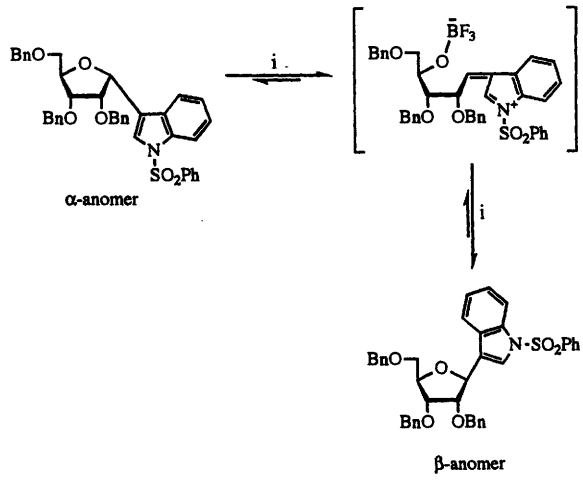


Fig. 1 Reaction temperature dependence of β-selectivity



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

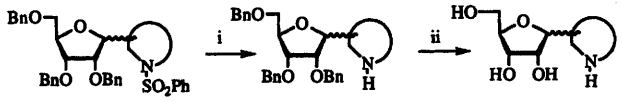
[a] Reaction conditions: $EtNO_2$, BF_3·OEt_2, 0.5 h.

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].

Acknowledgements

This work was supported by a Grant-in-Aid No.07554085 for Scientific Research from the Ministry of Education, Science and Culture, Japan. We thank Dr T. Watanabe (Faculty of Pharmaceutical Science, Chiba University) for the gift of indoles.

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.

Paper 6/02020H
Received 22*nd March* 1996
Accepted 21*st May* 1996