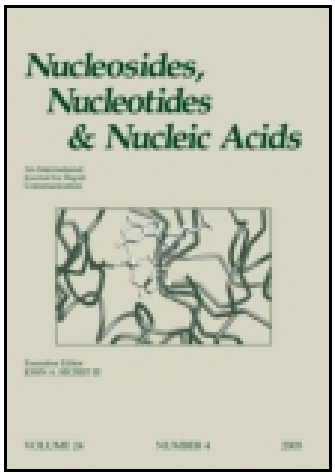

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

Regioselective Synthesis of Indazole N ^{1}- and N ^{2}-(β-d-Ribonucleosides)

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Published online: 01 Jun 2007.

To cite this article: Frank Seela & Xiaohua Peng (2004) Regioselective Synthesis of Indazole N ^{1}- and N ^{2}-(β-d-Ribonucleosides) , Nucleosides, Nucleotides and Nucleic Acids, 23:1-2, 227-237, DOI: 10.1081/NCN-120027830

To link to this article: http://dx.doi.org/10.1081/NCN-120027830

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 1 & 2, pp. 227–237, 2004

Regioselective Synthesis of Indazole N^1- and N^2-(β-D-Ribonucleosides)†

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ABSTRACT

The regioselective synthesis of 4-nitroindazole N^1- and N^2-(β-D-ribonucleosides) (**8**, **9**, **1b** and **2b**) is described. The N^1-regioisomers are formed under thermodynamic control of the glycosylation reaction [fusion reaction or Silyl Hilbert-Johnson glycosylation for 48 h (66%)], while the kinetic control (Silyl Hilbert-Johnson glycosylation for 5 h) afforded only the N^2-isomer (64%). The structures of the nucleosides **1b** and **2b** were assigned by single crystal X-ray analyses. The 4-amino-N^1-(β-D-ribofuranosyl)-1*H*-indazole (**3b**) was obtained from the nitro nucleoside **1b** by catalytic hydrogenation. Compound **3b** shows fluorescence while the 4-nitroindazole nucleosides **1b** and **2b** do not possess this property.

Key Words: Glycosylation; 4-Nitroindazole; Ribonucleosides; Fluorescence; Regioselectivity.

†In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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DOI: 10.1081/NCN-120027830 1525-7770 (Print); 1532-2335 (Online)

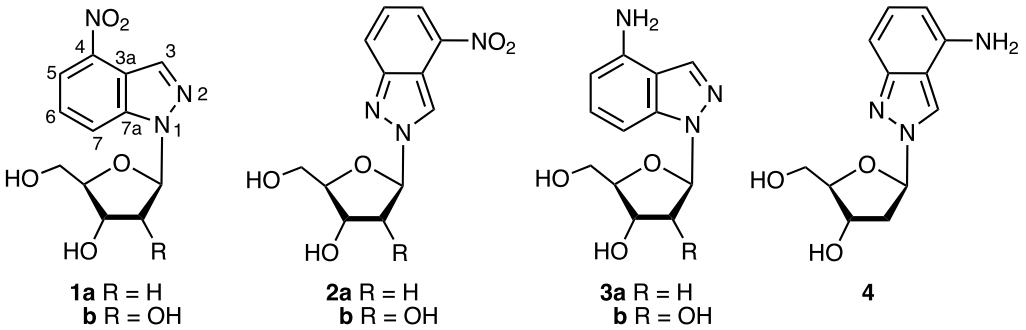
INTRODUCTION

During the last years, the study of indazoles[1] has received considerable attention because 1*H*-indazole is structurally related to 1*H*-benzimidazole,[2] and many indazoles exhibit biological[3] or antiallergic activity[4] or function as antagonists of serotonine receptors.[5] A series of indazole nucleosides have already been synthesized, including indazole, 4-, 5-, 6-nitroindazole,[6–11] halogenated indazole ribonucleosides,[12] and the 2′-deoxyribonucleosides of 4-nitro and 4-aminoindazole.[13,14] In general, both N^1- and N^2-isomeric nucleosides can be obtained by thermodynamic or by kinetic control of the glycosylation reaction, respectively. However, in the case of 4-nitroindazole ribonucleosides, only the N^2-glycoside has been reported[6] while the N^1-isomer is unknown. This prompted the present investigation in an effort to study the reaction conditions in more detail and to synthesize 4-nitro-1-(β-D-ribofuranosyl)-1*H*-indazole (**1b**) and the corresponding amino derivative **3b**.

Earlier, we have reported on the synthesis of the 4-nitroindazole 2′-deoxyribonucleosides **1a** and **2a**, as well as the 4-aminoindazole 2′-deoxyribonucleosides **3a** and **4** (Scheme 1).[13] Meanwhile, the ambiguous nature in oligonucleotide base pairing and the influence of the glycosylation position on the duplex stability have been studied.[14] In this paper, our work focuses on the study of the fusion method and the Silyl-Hilbert-Johnson reaction with respect to the synthesis of the 4-nitroindazole N^1-(β-D-ribonucleoside) **1b** and the N^2-(β-D-ribonucleoside) **2b**. The determination of the glycosylation position and the assignment of the anomeric configuration were ascertained by single crystal X-ray analyses. Furthermore, the fluorescence of the target compounds was detected.

RESULTS AND DISCUSSION

From previous investigations on indazole nucleosides it has been observed that the formation of regioisomeric glycosylation products depends on the particular reaction conditions and on the structure of the precursors. The silyl method or the $Hg(CN)_2$-CH_3NO_2-mediated reaction afforded the N^2-glycosylated indazoles, exclusively.[6–8,15] On the other hand, the corresponding N^1-glycosylated indazoles were formed under



Scheme 1. Indazole nucleosides.

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Scheme 2. The Silyl-Hilbert-Johnson glycosylation.

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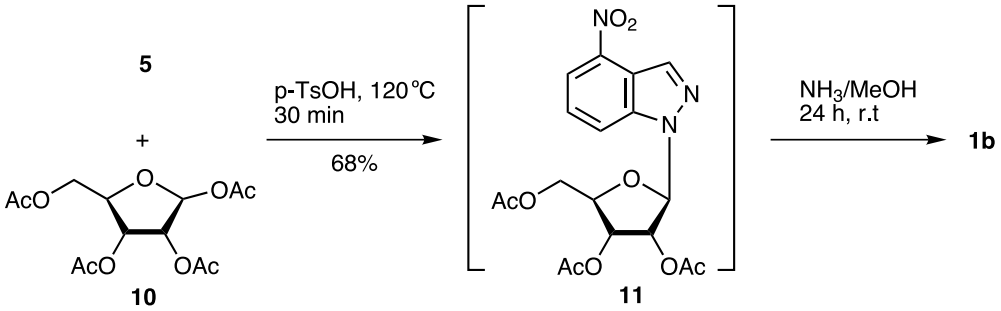
conditions of the fusion reaction using peracylated D-ribose derivatives.[9–12,16,17] Now, the regioisomers **1b** and **2b** were obtained under different reaction conditions (Scheme 2). The silylation of 4-nitro-1*H*-indazole (**5**)[18] furnished N-trimethylsilylated 4-nitroindazole (**6**) in quantitative yield. At first, the glycosylation of **6** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (**7**) in dichloroethane with TMSOTf as catalyst, was investigated at different temperatures and reaction times. The reaction performed at room temperature within two days affording 4-nitro-1-[(2,3,5-tri-*O*-benzoyl)-*β*-D-ribofuranosyl]-1*H*-indazole (**8**) as the major product (66%) and only traces of 4-nitro-2-[(2,3,5-tri-*O*-benzoyl)-*β*-D-ribofuranosyl]-2*H*-indazole (**9**). If the reaction was performed only for 5 hours, the nucleoside **9** was isolated (64%). The glycosylation reaction was monitored by TLC (CH_2Cl_2/AcOEt, 99:1). In the initial stages of the reaction only a slow migrating spot was observed assigned to the N^2-isomer **9**. When the reaction progressed, the TLC showed two spots with a gradually diminished slow migrating component. Later, the less polar product was formed which is the N^1-isomer **8**. When the coupling proceeded higher than 50°C, compound **8** was obtained exclusively after one day. Compounds **8** and **9** were deprotected with methanolic ammonia affording the indazole ribonucleosides **1b** and **2b**, respectively. The nitro nucleoside **1b** was hydrogenated under normal pressure (Pd/C) to give the amino nucleoside **3b**. Compound **2b** could not be hydrogenated under the same conditions.

The most likely explanation for the formation of nucleosides **8** and **9** under different conditions (reaction time and temperature) is a two step glycosylation reaction. In the first step, the reaction of the silylated base and a sugar cation leads to the kinetically controlled product **9**. When the reaction temperature is increased or the reaction time is prolonged, compound **9** undergoes a rearrangement to form the thermodynamically more stable isomer **8**.

Compound **1b** was also synthesized by the fusion reaction (Scheme 3). The fusion of non-silylated **5** with tetra-*O*-acetyl-*β*-D-ribofuranose (**10**) in *vacuo* at 120°C in the presence of *p*-toluenesulfonic acid gave exclusively 4-nitro-1-[(2,3,5-tri-*O*-acetyl)-*β*-D-ribofuranosyl]-1*H*-indazole (**11**), which was directly deacetylated with methanolic ammonia furnishing the nucleoside **1b** in 68% yield. The fusion of the silylated 4-nitroindazole **6** with **10** (same conditions) resulted in a mixture of N^1 and N^2-isomers. They were deprotected without isolation of the intermediates to give a mixture of **1b/2b** (ratio = 2.6:1, determined from ^{1}H-NMR spectra). A selective formation of the



Scheme 3. The synthesis of 4-nitroindazole N^1-(*β*-D-ribonucleosides) by fusion reaction.

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Table 1. ^{13}C-NMR chemical shifts of indazole ribonucleosides.[a]

Compound	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
1b	133.1	116.6	141.5	119.0	126.5	118.1	139.7
2b	124.0	113.5	140.3	120.8	125.1	126.5	149.1
3b	132.9	114.0	142.4	102.2	128.2	96.2	141.7
5	132.5	115.3	141.5	118.4	125.7	118.2	139.6
8	133.5	116.6	141.5	119.4	127.1	118.0	139.9
9	125.9	113.5	149.8	121.4	126.3	126.5	140.4
	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	3C═O	
1b	90.5	73.5	70.6	85.2	62.0		
2b	95.1	75.7	69.9	85.5	61.0		
3b	89.9	73.2	70.8	84.6	62.4		
8	88.0	71.1	74.5	79.2	62.9	165.3, 164.8, 164.6	
9	91.8	71.1	75.1	79.9	63.0	165.3, 164.7, 164.4	

[a]Measured in DMSO.

N^2-isomer was reported by Revankar and Townsend using 2,3,5-tri-*O*-acetyl-α-D-ribofuranosyl bromide[19] in the fusion reaction.[6]

All compounds were characterized by elemental analysis as well as by ^{1}H- and ^{13}C-NMR. The ^{13}C-NMR signals were assigned by gated-decoupled ^{13}C-NMR spectra. The ^{13}C-NMR signal of the C (7) was shifted downfield about 8 ppm, while an upfield shift of C(3) by 9 ppm was found when the glycosylation position changed from N(1) to N(2) (Table 1).

All other ^{13}C-NMR shifts were assigned by comparison of the NMR data shown in Table 1 with those of 4-nitroindazole 2′-deoxyribonucleosides, which were assigned by NOE experiments followed by ^{1}H, ^{13}C NMR-correlation spectra.[13] Similar to 4-nitroindazole 2′-deoxyribonucleosides, the N^2-isomers **9** and **2b** show a significant downfield shift of the H-C(3) (about 0.50 ppm) compared to N^1-isomer **8** and **1b**.

The crystal structures of **1b** (Figure 1) and **2b** (Figure 2) were also determined confirming the assignment of the anomeric configurations as well as the glycosylation

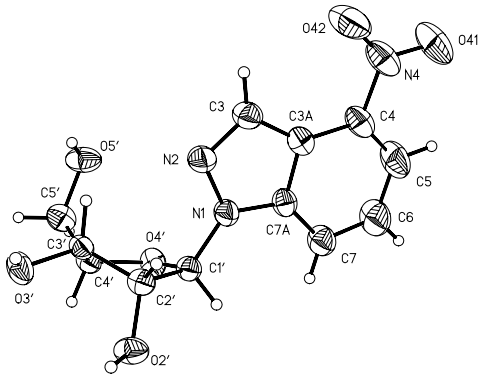

Figure 1. Perspective view of compound **1b**.

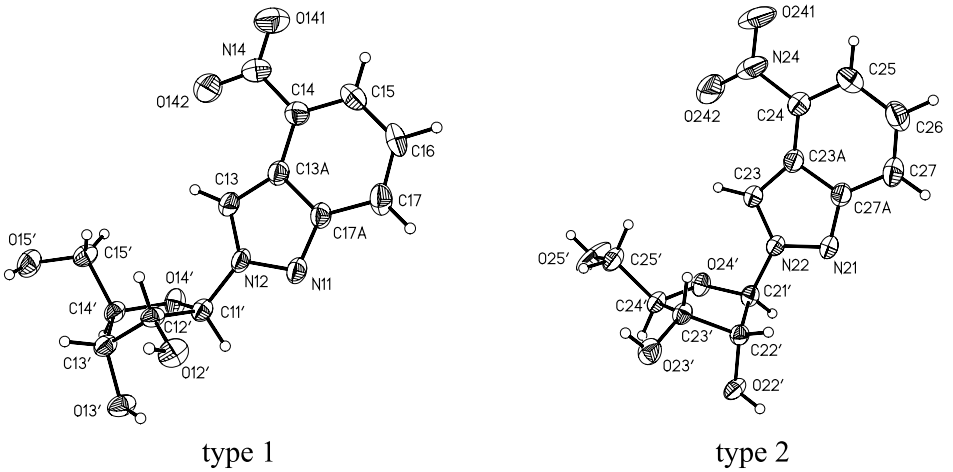

Figure 2. Perspective view of compound **2b**. Type 1: *S*-conformation; type 2: *N*-conformation.

sites. Compound **2b** shows two conformations in the crystalline state which differ mainly in the sugar conformation. Type 1 adopts an *S*-type conformation; type 2 shows an *N*-type conformation (Figure 2). Details will be published elsewhere.[20]

The photophysical properties of the compounds **1b**, **2b** and **3b** in solution were also studied. The UV/Vis absorption spectra are shown in Figure 3(A). At room temperature no fluorescence could be detected for **1b** and **2b** due to the presence of nitro substituents quenching the fluorescence efficiently. Nevertheless, nucleoside **3b** shows strong fluorescence. According to Figure 3(B), the emission spectrum of **3b** exhibits a broad emission band with a maximum at 400 nm. The excitation spectrum of **3b** is very similar to its absorption spectrum, indicating that the sample is sufficiently pure and that the excited singlet state is the origin of the observed emission.

CONCLUSION

The indazole N^1-ribonucleoside **1b** was prepared selectively via the fusion reaction, while the Silyl Hilbert-Johnson glycosylation performed for 5 h furnished the N^2-nucleoside **2b**. Both nucleoside structures were established by single crystal X-ray analyses. The amino nucleoside **3b** shows strong fluorescence.

EXPERIMENTAL PART

General. Chemicals and solvents are of laboratory grade. Flash chromatography (FC): at 0.6 bar on silica gel 60H (VWR, Germany); Thin-layer chromatography (TLC): aluminum sheets coated with silica gel 60 F_{254} (VWR, Germany). Mp.: SMP-20 apparatus (*Büchi*, Switzerland). UV Spectra: U-3200 spectrophotometer (*Hitachi*, Japan). NMR spectra: *Avance-DPX-250*, *Brucker-AC-250* and *AMX-500* spectrometer;

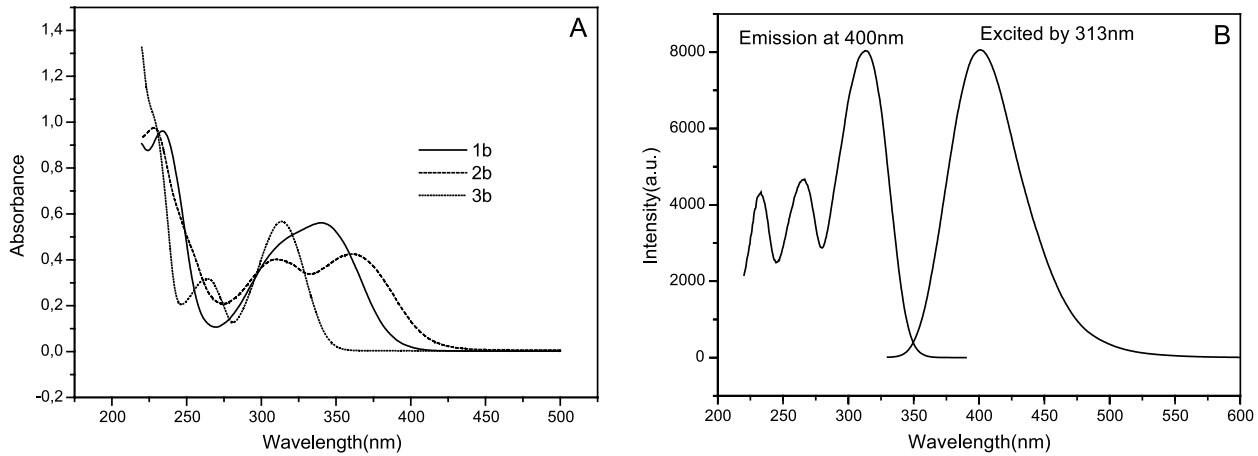

Figure 3. A: The absorption spectra of compounds **1b**, **2b**, **3b** at room temperature. B: The emission and excitation spectra of **3b** at room temperature. Solvent: methanol; concentration: $C_{\mathbf{1b}} = 8.25 \times 10^{-5}$ M, $C_{\mathbf{2b}} = 6.64 \times 10^{-5}$ M, $C_{\mathbf{3b}} = 6.83 \times 10^{-5}$ M.

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δ values in ppm rel. to internal Me_4Si, J values in Hz. Fluorescence spectra: F-4500 spectrometer (*Hitachi*, Japan). Elemental analyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, Germany.

4-Nitro-1-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-1*H*-indazole (8). A mixture of dry 4-nitro-1*H*-indazole[18] (**5**) (652 mg, 4.0 mmol) and a catalytic amount of ammonium sulfate (15 mg) was refluxed in hexamethyldisilazane (15.0 mL, 72.76 mmol) with the exclusion of moisture for 20 h. After removal of the solvent, the resulting semi-solid trimethylsilyl 4-nitro-1*H*-indazole (**6**) was suspended in dry dichloroethane (20.0 mL). Into this mixture, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**) (2.27 g, 4.5 mmol)[21] and TMSOTf (0.95 mL, 5.46 mmol) were added, yielding a clear solution which was stirred at room temperature for 48 h. It was diluted with dichloromethane (50 mL), washed with aq. saturated sodium bicarbonate (20 mL); and the organic phase was washed with water. The solution was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure to give a syrup, which was applied to FC on a silica gel (column 4 × 12 cm, solvent CH_2Cl_2). The main zone afforded compound **8** as yellowish foam (1.60 g, 66%). R_f 0.35 (CH_2Cl_2/AcOEt, 99:1); UV (MeOH) λ_{max} = 229 nm (ε 48600), 282 nm (ε 6100), 340 nm (ε 6600); ^{1}H NMR (DMSO-d_6) δ 4.49–4.52 (dd, J = 3.5, 12.3, 1 H, H-5′), 4.68–4.71 (dd, J = 2.8, 12.2, 1 H, H-5′), 4.95 (m, 1 H, H-4′), 6.27 (t, J = 6.1, 1 H, H-3′), 6.41 (t, J = 3.7, 1 H, H-2′), 7.13 (s, 1 H, H-1′), 7.47–7.54 (m, 6 H, arom), 7.64–7.69 (m, 3 H, arom), 7.74 (t, J = 7.7, 8.5, 1 H, H-6), 7.8 (m, 2 H, arom), 7.95–7.99 (m, 4 H, arom), 8.22 (d, J = 7.7, 1 H, H-5), 8.48 (d, J = 8.5, 1 H, H-7), 8.66 (s, 1 H, H-3); Anal. Calc. for $C_{33}H_{25}N_3O_9$ (607.6): C 65.24, H 4.15, N 6.92, found C 65.28, H 4.21, N 7.02.

4-Nitro-2-[(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl]-2*H*-indazole (9). A mixture of **5** (128 mg, 0.79 mmol) and a catalytic amount of ammonium sulfate (10 mg, 0.76 mmol) in hexamethyldisilazane (4.0 mL, 19.40 mmol) was refluxed under the protection of Ar for 20 h. After evaporation of the solvent, the resulting semi-solid material was suspended in dry dichloroethane (5.0 mL). Into this reaction mixture, **7** (395 mg, 0.78 mmol) and TMSOTf (0.2 mL, 1.15 mmol) were added, giving a clear solution which was stirred at room temperature for 5 h. The reaction mixture was diluted with dichloromethane (5 mL), washed with aq. saturated sodium bicarbonate (5 mL) and then with water. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to give a syrup, which was applied to FC on silica gel (column: 4 × 9 cm, CH_2Cl_2). The main zone afforded compound **9** as a yellowish foam (306 mg, 64%). R_f 0.31 (CH_2Cl_2/AcOEt, 99:1); UV (MeOH) λ_{max} 229 nm (ε 48600), 273 nm (ε 4300), 282 nm (ε 4400), 312 (ε 5600), 355 (ε 6500); ^{1}H NMR (DMSO-d_6) δ 4.57–4.64 (dd, J = 4.1, 12.4, 1 H, H-5′), 4.76–4.82 (dd, J = 3.1, 12.3, 1 H, H-5′), 5.03 (m, 1 H, H-4′), 6.31 (m, 2 H, H-2′, H-3′), 6.99 (s, 1 H, H-1′), 7.44–7.68 (m, 10 H, H-6, arom), 7.69–7.98 (m, 6 H, arom), 8.15 (t, J = 7.7, 8.5, 1 H, H-5), 8.25 (d, J = 8.3, 1 H, H-7), 9.20 (s, 1 H, H-3); Anal. Calc. for $C_{33}H_{25}N_3O_9$ (607.6): C 65.24, H 4.15, N 6.92, found C 65.28, H 4.20, N 6.88.

4-Nitro-1-(β-D-ribofuranosyl)-1*H*-indazole (1b). Compound **8** (1.0 g, 1.65 mmol) was dissolved in methanolic ammonia (methanol saturated with ammonia at

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0°C, 30 mL) and stirred at room temperature for 24 h. After removal of the solvent, the residue was dissolved in MeOH and adsorbed on a small amount (4.0 g) of silica gel. This material was loaded on the top of a silica gel column (4 × 15cm), and the product was eluted stepwise with CH_2Cl_2/MeOH (98:2, 300 mL) and CH_2Cl_2/MeOH (9:1, 600 mL). The product-containing fractions were combined and evaporated to give a semi-solid, which was crystallized from MeOH furnishing yellowish needles (433 mg, 89%). Mp. 176–177°C; R_f 0.35 (CH_2Cl_2/MeOH, 9:1); UV (MeOH) λ_{max} 235 nm (ε 11000) 340 nm (ε 6800); ^{1}H NMR (DMSO-d_6) δ 3.43–3.47 (m, 1 H, H-5′); 3.54–3.61 (m, 1 H, H-5′); 3.94–4.00 (q, J = 4.8, 1 H, H-4′); 4.23–4.29 (q, J = 5.1, 1 H, H-3′); 4.65–4.71 (q, J = 5.0, 1 H, H-2′); 4.82–4.86 (t, J = 5.5, 1 H, OH-5′); 5.24 (d, J = 5.4, 1 H, OH-2′); 5.48 (d, J = 5.8, 1 H, OH-3′); 6.25 (d, J = 4.5, 1 H, H-1′); 7.68 (t, J = 8.1, 1 H, H-6); 8.21 (d, J = 7.7, 1 H, H-5); 8.42 (d, J = 8.5, 1 H, H-7); 8.63 (s, 1 H, H-3); Anal. Calc. for $C_{12}H_{13}N_3O_6$ (295.25): C 48.82, H 4.44, N 14.23, found C 49.15, H 4.51, N 14.02.

4-Nitro-2-(β-D-ribofuranosyl)-2*H*-indazole (2b). Compound **9** (280 mg, 0.46 mmol) was dissolved in methanolic ammonia (20 mL) and stirred at room temperature overnight. After removal of the solvent, the residue was dissolved in MeOH and adsorbed on a small amount (2.0 g) of silica gel. This material was loaded on the top of a silica gel column (3 × 9 cm), and the product was eluted stepwise with CH_2Cl_2/MeOH (98:2, 100 mL) and CH_2Cl_2/MeOH (9:1, 200 mL). The product-containing fractions were combined and evaporated to give a semi-solid, which was crystallized from MeOH. Yellowish needles (125 mg, 92%). Mp. 172–173°C; R_f 0.35 (CH_2Cl_2:MeOH, 9:1); UV(MeOH) λ_{max} 230 nm (ε 8600), 314 nm (ε 5500), 359 nm (ε 6400); ^{1}H NMR (DMSO-d_6) δ 3.59–3.64 (m, 1 H, H-5′), 3.70–3.74 (m, 1 H, H-5′), 4.05 (q, J = 4.8, 1 H, H-4′), 4.24 (q, J = 5.1, 1 H, H-3′), 4.42 (q, J = 3.6, 1 H, H-2′), 5.11 (t, J = 5.3, 1 H, OH-5′), 5.24 (d, J = 5.7, 1 H, OH-3′), 5.66 (d, J = 5.6, 1 H, OH-2′), 6.12 (d, J = 3.5, 1 H, H-1′), 7.54 (t, J = 8.1, 1 H, H-6), 8.21 (d, J = 7.7, 1 H, H-5, H-7), 9.21 (s, 1 H, H-3); Anal. Calc. for $C_{12}H_{13}N_3O_6$ (295.25): C 48.82, H 4.44, N 14.23, found C 48.79, H 4.31, N 14.15.

4-Nitro-1-(β-D-ribofuranosyl)-1*H*-indazole (1b) (Fusion reaction, one step procedure). A mixture of compound **5** (652 mg, 4.0 mmol), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**10**, 1.53 g, 4.8 mmol)[22,23] and *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.079 mmol) was heated to 100–130°C for 30 min under vacuo. The dark melt was dissolved in methanolic ammonia (30 mL), and stirred at r.t. overnight. The solution was evaporated to dryness, redissolved in MeOH (10 mL) and adsorbed on a small amount (5.0 g) of silica gel. This material was loaded on the top of a silica gel column (4 × 15 cm), and the product was eluted with a stepwise gradient CH_2Cl_2/MeOH (98:2, 300 mL) and CH_2Cl_2/MeOH (9:1, 600 mL). The product-containing fractions were combined and evaporated to give a semi-solid, which was crystallized from MeOH. Yellowish needles (800 mg, 68%). The NMR data are identical to those obtained from the compound synthesized by the Silyl-Hilbert-Johnson glycosylation followed by deprotection.

4-Amino-2-(β-D-ribofuranosyl)-2*H*-indazole (3b). Compound **1b** (200 mg, 0.68 mmol), dissolved in EtOH (20 mL), was hydrogenated for 4h in the presence of 10% Pd/C (200 mg) at r.t./1 atm. The catalyst was filtered off and washed with EtOH. The

solvent was evaporated, the residue was dissolved in MeOH and adsorbed on a small amount (3.0 g) of silica gel. This material was loaded on the top of a silica gel column (2.0 × 6 cm), and the product was eluted stepwise with CH_2Cl_2/MeOH (95:5, 100 mL) and CH_2Cl_2/MeOH (9:1, 100 mL). The product-containing fractions were combined and evaporated to give a foam, which was crystallized from MeOH. Yellowish needles (129 mg, 72%). Mp. 151–152°C; R_f 0.25 (CH_2Cl_2/MeOH, 9:1); UV (MeOH) λ_{max} 264 nm (ε 4900), 312 (ε 8300); ^{1}H NMR (DMSO-d_6) δ 3.42 (m, 1 H, H-5′), 3.54 (m, 1 H, H-5′), 3.88 (m, 1 H, H-4′), 4.20 (m, 1 H, H-3′), 4.60 (m, 1 H, H-2′), 4.77 (t, J = 5.6, 1 H, OH-5′), 5.12 (d, J = 5.6, 1 H, OH-2′), 5.32 (d, J = 5.8, OH-3′), 5.76 (s, 2 H, NH_2), 5.92 (d, J = 4.2, 1 H, H-1′), 6.20 (d, J = 7.5, 1 H, H-5), 6.75 (d, J = 8.2, 1 H, H-7), 7.05 (t, J = 8.2, 1 H, H-6), 8.18 (s, 1 H, H-3); Anal. Calc. for $C_{12}H_{15}N_3O_4$ (265.3): C 54.33, H 5.70, N 15.84, found C 54.32, H 5.56, N 15.78.

ACKNOWLEDGMENTS

The authors thank Dr. H. Rosemeyer and Dr. Y. He for the measurement of the ^{1}H- and ^{13}C-NMR spectra. We gratefully acknowledge financial support by the European Community (grant no.: QLRT-2001-00506, ''Flavitherapeutics'').

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Received August 22, 2003
Accepted October 6, 2003

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