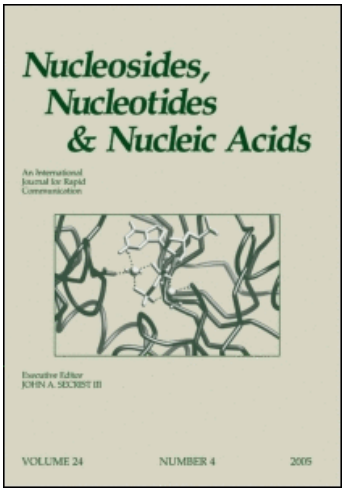

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O-GLYCOSIDES OF *N*-HYDROXYINDOLES[1]

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O-GLYCOSIDES OF *N*-HYDROXYINDOLES[1]

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ABSTRACT

First *O*-glycosides of *N*-hydroxyindole were synthesized by the interaction of the indoles containing electron withdrowing substituents with acyl halogenoses in the presence of alkaline reagents. 1-*O*-β-D-Glucopyranosides of 1-hydroxy-5-(or 6)-nitroindoles, 1-*O*-β-D-ribofuranoside of 1-hydroxy-5-nitroindole and also 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-2-methoxycarbonylindole were obtained. 1-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-oxy]-6-nitro-indole was transformed into 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-oxy]indole.

Methods of synthesis of indole *N*-nucleosides have been extensively elaborated[2]. The investigation of these analogs of nucleic acid components revealed nitroindole derivatives that are currently employed in the investigation of nucleic acid biochemistry[3]. In the course of our project on the study of *N*-hydroxyindole properties we are studying methods of synthesis and some properties of *O*-glycosides of *N*-hydroxyindoles. These *O*-glycosides are also of interest as starting compounds in the synthesis of *N*-glycosyloxy analogs of biologically important *N*-glycosylindole antibiotics (e.g. analogs of rebeccamycin, staurosporine and related compounds)[4].

1-Hydroxyindoles recently became available due to the pioneering study of M. Somei and co-workers[5], who have developed several methods of synthesis of *N*-hydroxyindoles, among which the most convenient method is

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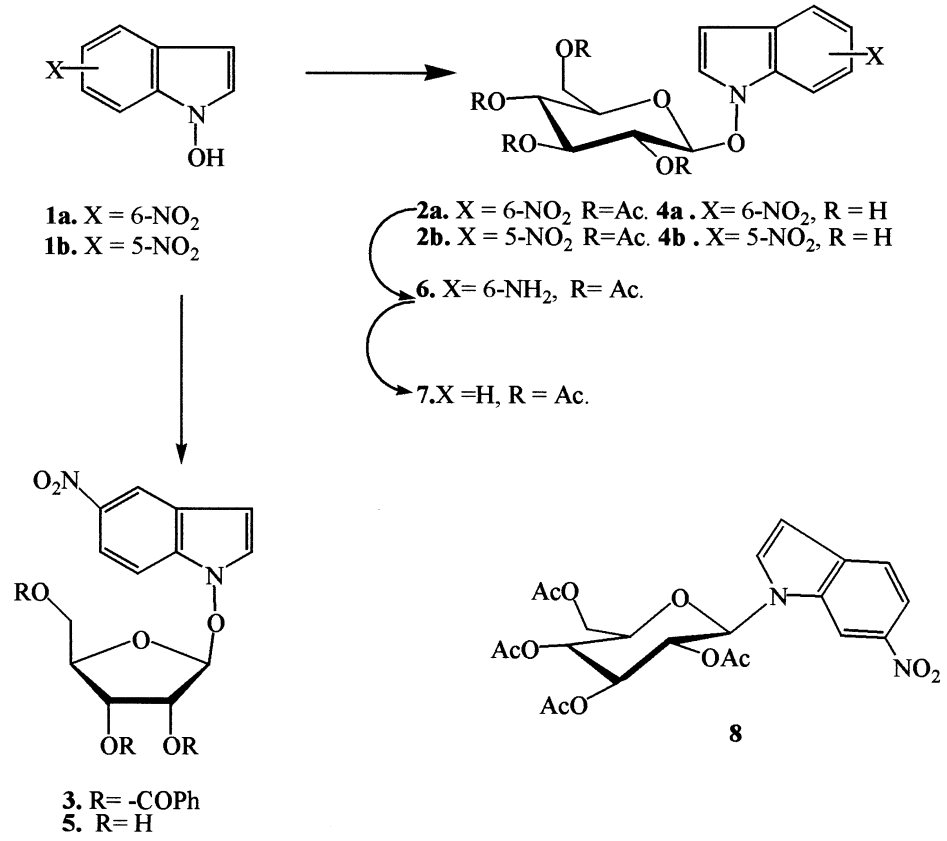
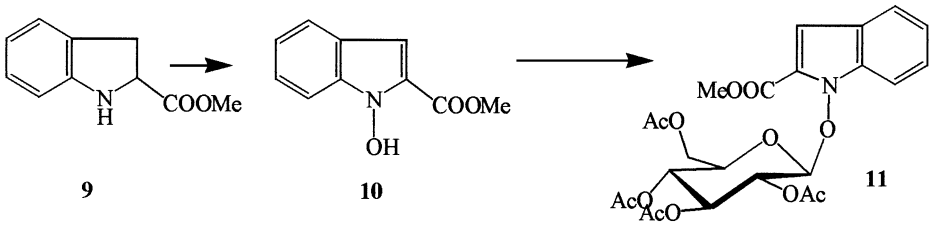
based on the oxidation of indoline by H_2O_2 in the presence of Na_2WO_4. 1-Hydroxyindoles with electron withdrowing substituents are rather stable and can be used in further transformations. We have found that 6- or 5-nitro derivatives of 1-hydroxyindole (**1a** or **b**) can be glycosylated in the conditions used for the glycosylation of phenols. Per-*O*-acylated 1-[(glycosyl)oxy]-5-nitroindoles (**2b** or **3**) were obtained in 70–75% yields by the condensation of 1-hydroxy-5-nitroindole (**1b**) with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide or 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetone and in the presence of K_2CO_3. *O*-Deacylation led to the corresponding *O*-deprotected 1-*O*-β-D-glucopyranoside **4b** or 1-*O*-β-D-ribofuranoside **5**. Similarly, the 1-*O*-β-D-glucopyranoside of 1-hydroxy-6-nitroindole (**4a**) was obtained from 1-hydroxy-6-nitroindole (**1a**) *via* 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glycosyl)oxy]-6-nitroindole (**2a**).

Our attempts to use this method, along with the use of Ag_2O or Ag_2CO_3 as alternative bases, for the *O*-glycosylation of unsubstituted



Scheme 1.



Scheme 2.

1-hydroxyindole were unsuccessful. The 1-*O*-tetraacetyl-β-D-glucopyranoside of 1-hydroxyindole (7) was obtained by an indirect method in which 6-nitro compound **2a** was reduced by Zn powder in HCl to give the amino-compound **6**, which was deaminated without isolation by the diazotization and consequent reduction of the formed diazonium derivative by boiling in aqueous ethanol to produce 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]indole (7) in 61% summary yield. As not in this study indole *N*-nucleoside 1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-nitroindole **8** was synthesised by the method described[6] to allow a comparison to be made of the NMR parameters of both *O*- and *N*-indole nucleosides.

1-Hydroxy-2-methoxycarbonylindole (**10**) was obtained in 65% yield by the oxidation of 2-methoxycarbonylindoline (**9**) using standard conditions[5]. Reaction of **10** with α-acetobromoglucose in the presence of K_2CO_3 and acetone gave 2-methoxycarbonyl-1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]indole (**11**) in 70% yield.

The β-configuration and $^4C_1$ conformation (for glucopyranosides) was confirmed by ^{1}H NMR data (see Tables 1 and 2)[7]. A comparison of the ^{1}H NMR parameters of glycosyloxy derivative **2a** with those of *N*-glucopyranosyl-6-nitroindole **8** shows, that the chemical shifts for *N*-glycosylindoles and *N*-glycosyloxyindoles are rather similar, except for the signal of 2-H, which appears 0.23 ppm lower field than that of **8**. In ^{13}C NMR spectra of *N*-glycosyloxyindoles (Table 3) the position of C-1′ carbon atom is shifted downfield by $\sim$20 ppm in comparison with C-1′ signal of the *N*-glycosylindole **8**.

EXPERIMENTAL

NMR spectra were registered on a Varian VXR-400 instrument operated at 400 MHz (^{1}H NMR) or at 100.6 MHz (^{13}C NMR). Chemical shifts were measured in CD_3OD or $CDCl_3$ using these solvents as internal standards ($CDCl_3$: δ ^{1}H (residual) 7.25 ppm, ^{13}C 77.00 ppm; CD_3OD δ: ^{1}H (residual) 3.32 ppm, ^{13}C 49.00 ppm). Analytical TLC was performed on

Table 1. ^{1}H NMR Spectra (Chemical Shifts, ppm and Coupling Constants, Hz) of **2a**, **2b**, **4a**, **4b**, **7, 8, 11**

	Indole Ring						Carbohydrate Moiety							
Compound (Solvent)	2-H ($J_{2,3}$)	3-H ($J_{3,2}$)	4-H ($J_{4,5}$) [$J_{4,6}$]	5-H ($J_{5,6}$) [$J_{5,7}$] {$J_{5,4}$}	6-H ($J_{6,5}$) [$J_{6,4}$] {$J_{6,7}$}	7-H ($J_{7,6}$) [$J_{6,4}$]	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H ($J_{3,4}$)	4-H ($J_{4,5}$)	5-H	6-H_a ($J_{6a,b}$ $J_{6a,5}$)	6-H_b ($J_{6b,a}$ $J_{6b,5}$)	OAc or (COOMe) (singlet)
2a (CD_3OD)	7.71 d (3.5)	6.57 d (3.5)	7.72 d (8.7)	7.99 dd {8.7} [2.2]	–	8.39 d [2.2]	5.49 d (8.3)	5.27 dd (8.3; 9.5)	5.40 t (9.5)	5.18 t (9.5)	3.97 m	4.30 dd (12.4; 5.0)	4.16 dd (12.4; 2.3)	2.28 2.02 2.01 2.00
2b ($CDCl_3$)	7.39 d (3.5)	6.54 d (3.5)	8.50 d [2.0]	–	8.14 dd {9.0} [2.1]	7.40 d (8.9)	5.28 d (8.8)	5.16 m	5.27 t (5.0)	5.16 m	3.72 m	4.30 dd (12.5; 5.2)	4.13 dd (12.5; 2.4)	2.22 2.04 2.03 2.02
4a (CD_3OD)	7.84 d (3.4)	6.56 d (3.4)	7.64 d (8.7)	7.89 dd {8.7} [2.2]	–	8.63 d [2.2]	4.87 d (7.8)		3.46 m		3.33 m	3.87 dd (12.0; 2.4)	3.75 dd (12.0; 5.2)	–
4b (CD_3OD)	7.74 d (3.5)	6.60 d (3.5)	8.52 d [2.0]	–	8.00 dd {9.1} [2.0]	7.78 d (9.1)	4.74 d (7.7)		3.46 m		3.32 m	3.84 dd (12.1; 2.4)	3.75 dd (12.1; 5.1)	–
11 ($CDCl_3$)	–	7.09 s	7.53 d (8.0)	7.31 t (8.3)	7.14 t (8.0)	7.62 d (8.3)	5.53 d (8.2)	5.30 t (8.2)	5.39 t (9.4)	5.18 t (9.6)	3.74 m	4.32 dd (12.3; 5.4)	4.01 dd (12.3; 2.5)	2.14 2.03 2.02 1.89 (3.87)

8	7.48	6.65	7.64	8.05		8.41	5.67	5.48		5.32	4.06	4.31	4.18	2.09
	d	d	d	dd	–	d	d	m		t	m	dd	dd	2.07
($CDCl_3$)	(3.4)	(3.3)	(8.7)	{8.7}		[1.8]	(8.7)			(9.6)		(12.5; 4.6)	(12.5; 2.1)	2.01
				[2.0]										1.69
7	7.19	6.24	7.52	7.10	7.22	7.45	4.76	5.29	5.18	5.13	3.05	4.16	3.89	1.89
	d	d	d	t	t	d	d	dd	t	t	m	dd	dd	1.79
($CDCl_3$-C_6D_6,1:2)	(3.4)	(3.4)	(7.9)	(8.1)	(8.1)	(8.2)	(8.4)	(8.4; 9.5)	(9.3)	(9.3)		(12.5; 5.0)	(12.5; 2.2)	1.77
														1.71

Table 2. ^{1}H NMR Spectra (Chemical Shifts, ppm and Coupling Constants, Hz) of **3** and **5**

	Indole Moiety					Carbohydrate Moiety					
Compound (Solvent)	2-H ($J_{2,3}$)	3-H ($J_{3,2}$)	4-H ($J_{4,6}$)	6-H [$J_{6,4}$] {$J_{6,7}$}	7-H ($J_{7,6}$)	1-H ($J_{1,2}$)	2-H ($J_{2,3}$)	3-H ($J_{3,4}$)	4-H	5-H_a ($J_{a,b}$, $J_{5a,4}$)	5-H_b ($J_{5a,b}$, $J_{5b,4}$)
3*	7.48 d (3.5)	6.47 d (3.5)	8.46 d (2.0)	8.09 dd [2.0] {9.1}	8.07 d (9.1)	5.87 d (2.1)	6.01 dd (5.2)	5.92 t (5.2)	4.92 m	4.87 dd (12.3; 3.3)	4.65 dd (12.3; 4.3)
($CDCl_3$)											
5	7.77 d (3.5)	6.60 d (3.5)	8.55 d (2.1)	8.10 dd [2.2] {9.1}	7.65 d (9.1)	4.96 d (1.7)	4.36 dd (4.8; 11.7)	4.25 t (4.8)	4.14 m	3.85 dd (12.1; 3.5)	3.77 dd (12.1; 5.3)
(CD_3OD)											

*-signals of PhCOO groups are three multiplets in the regions 8.05–7.92; 7.6–7.5; 7.45–7.35.

Kieselgel F_{254} plates (Merck), preparative TLC on plates (20 × 20 cm, 0.5 mm) with Kieselgel 60 F_{254} (Merck) and column chromatography on silica gel 60 (Merck) in systems: petroleum ether-EtOAc 2:1 (A); 4:1 (B) or chloroform-methanol 5:1 (C). Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. UV spectra were recorded on a Hitachi-U 2000 spectrophotometer; $[\alpha]_D$ were measured on a polarimeter Perkin-Elmer 241. Electron impact mass-spectra (EI-MS) were obtained on an SAQ 710 Finnigan instrument at 70 eV (direct inlet, ion source temperature 150 °C). HRMS mass spectra were registered on a MAT 8430 Finnigan instrument with data operating system SS-300 (EI, 70 eV, direct introduction, temperature of ion source 250 °C). Electrospray ionization mass spectra (ESI MS) were obtained on Finnigan MAT 900S instrument. 2-Carboxyindoline used for the preparation of 2-methoxycarbonylindoline was purchased from Aldrich.

6-Nitro-1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]indole (2a). To a stirred suspension of anhydrous K_2CO_3 (4.6 g, 33.3 mmol) in 40 ml of dry acetone at room temperature was added 1-hydroxy-6-nitroindole (1.0 g, 5.6 mmol) and then 4.61 g (11.2 mmol) of α-D-acetobromoglucose, the reaction mixture was stirred for 15 h, diluted by EtOAc, washed by brine, dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography of the residue (A system) gave 2.15 g (75%) of **2a**, as a yellow powder. Mp 138–141 °C (EtOAc); R_f 0.32 (A); $[\alpha]_D^{20}$ −80.4° (c 0.5, $CHCl_3$). UV, λ_{max} nm (ε): 314 (8200), 249.5 (9900), 206 (18,700) ($CHCl_3$). EI-MS, *m/z* (%): 508 (M^+, 100); 449 (M^+-CH_3COO, 38).

Table 3. ^{13}C NMR Spectra of Compounds **2a, 2b, 3, 4a, 4b, 7, 8, 11**

Compound (Solvent)	C-NO_2 or (CCOOMe) atoms of indole	4a-C, 7a-C atoms of indole	C-H atoms of indole ring	1-C (glycosidic)	2, 3, 4, 5-C carbohydrate atoms	CH_2OH (COO-CH_3)	O-Ac or O-Bz
2a $CDCl_3$	143.88	131.66, 128.74	130.96, 121.32, 116.02, 105.56, 105.31	99.67	72.56, 69.64, 67.72, 63.32	61.32	170.50 20.62 170.08 20.61 169.31 20.52 169.26 20.51
2b $CDCl_3$	142.40	135.15 123.31	128.21, 118.31, 118.25, 108.51, 104.97	101.06	72.47 72.38, 69.57, 67.64	61.22	170.32 20.62 170.03 20.57 169.18 20.46 168.93 20.45
3 $CDCl_3$	142.27	134.98 123.21	133.88 133.71 133.40 111.02 108.55	100.99	81.41 73.89 71.22	63.55	165.99 165.22 165.12 129.75–129.59 128.57–128.41
4a CD_3OD	144.86	132.89 130.18	132.83, 122.01, 116.18, 109.91, 107.36	99.81	78.43, 77.91, 73.32, 70.87	62.34	
4b CD_3OD	143.44	136.78 124.76	130.34, 118.88, 118.57, 110.63, 109.92	101.43	78.41, 77.94, 73.33, 70.79	62.22	
7 $CDCl_3$		138.99 132.83	124.18 122.46 120.87 120.40 108.26 104.46	98.62	72.43 71.99 69.49 67.72	61.24	170.25 20.45 169.90 20.42 169.08 20.30 168.86 20.27
8 $CDCl_3$	143.62	134.591 33.86	130.06, 121.21, 116.17, 106.77, 104.74	83.59	74.91, 72.95, 70.39, 67.75	61.45	170.51 20.52 169.87 20.45 169.24 20.40 168.52 19.91
11 $CDCl_3$	(139.67)	127.98 122.45	126.27 122.23 121.99 112.60 110.18	104.75	72.51 71.71 69.62 68.48	61.62 (160.30 51.61)	170.36 20.66 169.91 20.48 169.58 20.40 169.36 20.38

5-Nitro-1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]indole (2b). 1-Hydroxy-5-nitroindole (0.5 g, 2.8 mmol) and α-D-acetobromoglucose (2.31 g, 5.6 mmol) gave 0.95 g (67%) of **2b** as a yellow powder. Mp 192–194 °C (EtOAc); R_f 0.3 (A); $[\alpha]_D^{20}$ − 33.6 ° (c 0.5, $CHCl_3$). UV, λ_{max} nm (ε): 316 (7700), 266 (20,300), 201 (17,800) ($CHCl_3$). EI-MS, *m/z* (%): 508 (M^+, 100); 449 (M^+-CH_3COO, 40).

1-[(β-D-Glucopyranosyl)oxy]-6-nitroindole (4a). To a stirred suspension of **2a** (1 g, 1.97 mmol) in 20 ml CH_3OH was added 1 ml of 1N CH_3ONa. After 30 min the solvent was evaporated, the residue was dissolved in 50 ml of water and passed through column with Dowex 50 × 8 (H^+), the eluate was evaporated to give 0.64 g (94%) of **4a** as a yellow powder. Mp 183-184 °C (CH_3OH); R_f 0.54 (C); $[\alpha]_D^{20}$ − 109.6 ° (c 0.5, CH_3OH). Anal. Calcd for $C_{14}H_{16}N_2O_8$ (340.29): C, 49.41; H, 4.74; N, 8.23. Found: C, 49.34; H, 4.71; N, 8.19. UV, λ_{max} nm (ε): 314.5 (6700), 253 (8300), 207 (16,300) (CH_3OH). EI-MS: *m/z* (%) 340 (M^+, 10); 178 (20); 162 (100); 145 (15); 132 (25); 116 (90).

1-[(β-D-Glucopyranosyl)oxy]-5-nitroindole (4b). 2b (0.7 g, 1.37 mmol) gave 0.45 g (97%) of **4b** as a yellow powder. Mp 149–150 °C (CH_3OH); R_f 0.52 (C); $[\alpha]_D^{20}$ − 62.8 ° (c 0.5, CH_3OH). Anal. Calcd for $C_{14}H_{16}N_2O_8$ (340.29): C, 49.41; H, 4.74; N, 8.23. Found: C, 49.40; H, 4.67; N, 8.17. UV, λ_{max} nm (ε): 320 (5300), 268.5 (14,100), 203 (13,600). ESI-MS: *m/z* (%): 363.3 ($M+Na^+$, 100); 379.4 ($M+K^+$, 35).

5-Nitro-1-[(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)oxy]indole (3). Compound **3** was synthesized from **1b** (1 g, 5.6 mmol), and tri-*O*-benzoyl-α-D-ribofuranosylbromide (5.9 g, 11.2 mmol); purification by column chromatography (B system) gave 1.78 g (51%) of **3** as a yellow foam, R_f 0.76 (A); $[\alpha]_D^{20}$ − 80 ° (c 0.5, $CHCl_3$); EI-MS: *m/z* (%) 622 (M^+, 100).

5-Nitro-1-[(β-D-ribofuranosyl)oxy]indole (5). Tribenzoate **3** (1 g) gave **5** (0.45 g, 90%) as a yellow foam, R_f 0.75 (C), $[\alpha]_D^{20}$ − 195.2 (c 0.5, CH_3OH); Anal. Calcd for $C_{13}H_{14}N_2O_7 \cdot H_2O$: C, 47.56; H, 4.91; N, 8.53. Found: C, 47.68; H, 5.00; N, 8.12. HRMS: Calcd ($C_{13}H_{14}N_2O_7$) 310.0801. Found 310.0848.

1-[(2,3,4,6-Tetra-I-acetyl-β-D-glucopyranosyl)oxy]indole (7). To a stirred solution of **2a** (250 mg, 0.49 mmol.) in THF (30 ml) at 0 °C was added 3 ml of 6M HCl, and then of Zn powder (290 mg, 4.43 mmol). After Zn was dissolved, ethanol (20 ml) was added, and the mixture was cooled to –5 °C, $NaNO_2$ (100 mg, 1.45 mmol) was added and the mixture was stirred for 10 min. Then the mixture was boiled for 20 min, diluted with brine (200 ml), the glycoside was extracted with EtOAc (70 ml), dried over Na_2SO_4, concentrated *in vacuo*, and purified by thick layer chromatography (A system)

to obtain **7** (139 mg, 61%) as light-brown syrup. R_f 0.68 (A); $[\alpha]_D^{20}$ $-42.6°$ (c 1, $CHCl_3$). HRMS: calcd for ($C_{22}H_{25}NO_{10}$) 463.1479. Found 463.1502.

1-Hydroxy-2-methoxycarbonylindole (10). To a stirred suspension of Na_2WO_4 (0.5 g in 50 ml) in water-methanol (90:1) was added 2-methoxycarbonylindoline (**9**) (2 g, 11.3 mmol). Then H_2O-H_2O_2, 8:28 ml (8 ml) was added dropwise during 40 min at 10–15 °C. The reaction mixture was partitioned between EtOAc and brine and the organic layer concentrated. Flash chromatography (B system) gave of yellow crystalline solid **10** (1.4 g, 65%). R_f 0.58 (A), mp 80–82 °C (EtOAc). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.79; H, 4.84; N, 7.28. EI-MS *m/z* (%): 191 (M^+,55); 175 [(M-Me+H)$^+$, 10]; 159 [(M-OMe+H)$^+$, 100]; 115 (80). ^{1}H NMR ($CDCl_3$): 10.19 (1H, s, -OH); 7.61 (1H, d, $J_{4,5}$ 9.07, H-4); 7.52 (1H, d, $J_{7,6}$ 9.38, H-7); 7.34 (1H, t, $J_{5,6}$ 8, H-5); 7.11 (1H, t, $J_{6,5}$ 8, H-6); 7.02 (1H, s, H-3); 3.98 (3H, s, -$COCH_3$).

2-Methoxycarbonyl-1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]indole (11). Compound **11** (1.9 g, 70% yield, white powder) was obtained and purified as for **2a** from **10** (1 g, 5.2 mmol) and α-D-acetobromoglucose (4.3 g, 10.4 mmol). Mp 96–99 °C ($CHCl_3$); R_f 0.25 (A); $[\alpha]_D^{20}$+45° (c 0.5, $CHCl_3$). Anal. Calcd for $C_{24}H_{27}NO_{12}$ (521.15): C, 55.26; H, 5.22; N, 2.69. Found: C, 55.26; H, 5.37; N, 2.61. EI-MS: *m/z* (%) 521 (M^+,5); 331 (50); 175 (25); 169 (100); 143 (40); 115 (60); 109 (55).

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