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Note

Direct C-glycosylation of indole with unprotected mono-, di-, and trisaccharides: a one-pot synthesis of 1-deoxy-1,1-bis(3-indolyl)alditols

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Abstract—1-Deoxy-1,1-bis(3-indolyl)alditols were synthesized by reacting 2.5 equiv of indole with 1 equiv of the following seven monosaccharides (D-galactose, D-mannose, D-allose, 2-deoxy-D-arabinohexose (2-deoxy-D-glucose), D-arabinose, L-arabinose, D-xylose), two disaccharides (D-lactose, D-maltose), and a trisaccharide (D-maltotriose) in 1:1 EtOH–H_2O at room temperature, or at 40 or 50 °C, in the presence of 5 mol % scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$], in a one-pot reaction, in 36–95% yields.

Keywords: Indole; Saccharides; Scandium(III) trifluoromethanesulfonate; Direct C-glycosylation; Alditol

In a previous paper,[1] we reported the synthesis of bis(3-indolyl)alkanes using 5 mol % $Sc(OTf)_3$[2] as a catalyst in aqueous media. This method permitted the reaction to proceed under mild, simple, and environmentally benign synthetic conditions. Under these conditions, indole reacted with unprotected sugars such as glucose and ribose to give 1-deoxy-1,1-bis(3-indoyl)alditols in yields of 82% and 78%, respectively, as reported previously.[3]

From the previous results, it would be predicted that, under these mild synthetic conditions, 2 equiv of indole would selectively react with the reducing terminus of 1 equiv of an oligosaccharide to give the corresponding 1-deoxy-1,1-bis(3-indoyl)alditol bearing O-glycopyranoside rings without breaking the O-glycosidic bond. We therefore examined the reaction of 2 equiv of indole with oligosaccharides such as lactose, maltose, and maltotriose. Furthermore, to explore steric or substituent effects of the sugar in this reaction, indole was reacted with the hexoses: D-galactose, D-mannose, D-allose, 2-deoxy-D-arabinohexose (2-deoxy-D-glucose), and 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine), and the pentoses: D- and L-arabinose, and D-xylose.[1]

The reaction was carried out in the same manner as described previously.[1] A solution of 2.5 equiv of indole and 1 equiv of sugar in 1:1 EtOH–H_2O was stirred at room temperature, or at 40 or 50 °C in the presence of 5 mol % $Sc(OTf)_3$. After acetylation [Ac_2O–pyridine–4-dimethylaminopyridine (DMAP)], each of the reaction products was purified, isolated, and structurally characterized, and the yields were determined. The results are summarized in Table 1.

All reactions of indole with hexoses (except for *N*-acetyl-D-glucosamine), in which the stereochemistry is different from D-glucose,[1] proceeded smoothly at 50 °C to give the corresponding alditols in 86%, 95%, and 82% yields (entries 1–3). The reaction with 2-deoxy-D-glucose at room temperature or 40 °C afforded the corresponding alditol in 43% or 33% yield, suggesting that the absence of a hydroxyl group at C-2 decreases the yield (entry 4). Thus the reaction using a 2-acetamido-2-deoxy sugar (*N*-acetyl-D-glucosamine) afforded many products, in which a small amount of the desired alditol was observed, with the remaining compounds being

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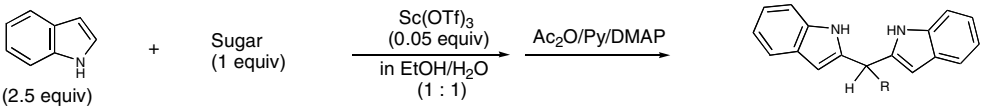
Table 1. Direct C-glycosylation of indole with mono-, di-, and trisaccharides



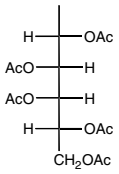
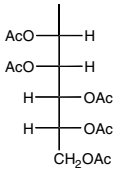
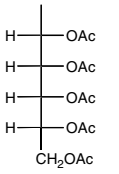
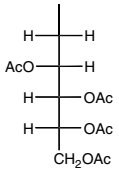
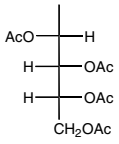
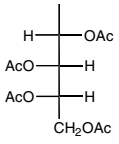
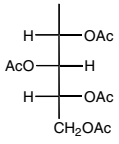
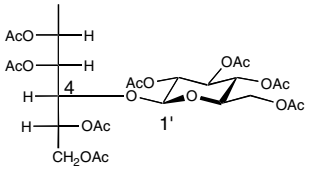
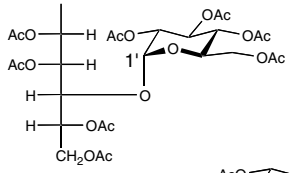
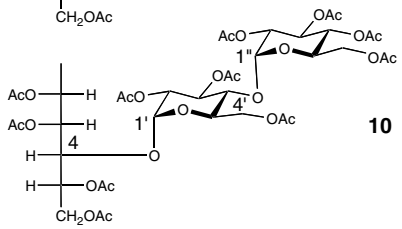
Entry	Sugar	Temp (°C)	Time (h)	Products (R=)	Yield (%)
1	D-Galactose	50	48	 **1**	86
2	D-Mannose	50	48	 **2**	95
3	D-Allose	50	48	 **3**	82
4	2-Deoxy-D-arabinohexose (2-deoxy-D-glucose)	rt 40	118 50	 **4**	43 33
5	D-Arabinose	40	20	 **5**	86
6	L-Aarabinose	rt	65	 **6**	83
7	D-Xylose	rt	68	 **7**	86
8	D-Lactose	50	40	 **8**	46

Table 1 (*continued*)

Entry	Sugar	Temp (°C)	Time (h)	Products (R=)	Yield (%)
9	D-Maltose	50	120	 **9**	56
10	D-Maltotriose	50	48	 **10**	36

compounds of other glycosides. Reactions of the three pentoses in which the stereochemistry of each is different from D-ribose[1] also proceeded smoothly at room temperature or 40 °C to give the corresponding alditols in 86%, 83%, and 86% yields (entries 5–7). The above results suggest that when a hydroxyl group at C-2 is replaced with another functional group, the yield of the 1-deoxy-1,1-bis(3-indoyl)alditol is decreased, and the pentose is more reactive than the hexose (Tables 2–7).

We next examined some reactions with di- and trisaccharides. The reaction of indole with two disaccharides, D-lactose and D-maltose, afforded the corresponding alditols as the sole products in 46% and 56% yields, respectively. Although the yields were lower than those for monosaccharides, the reactions proceeded regioselectively at the reducing terminal without cleavage of the β- or α-glycosidic bonds, since the NMR signals for H-4 were characteristically observed at higher fields of 4.17 and 4.00 ppm in an ^{1}H NMR analysis. Finally, the

Table 2. Physico-chemical property of compounds **1**–**10**

Compound no.		$[\alpha]_D$ ($CHCl_3$, temp °C)	IR ν (cm^{-1})	FAB (NBA, *m*/*z*) $(M+H)^+$	Elemental analysis (C, H, N %)
1	Pale brownish-white amorphous foam	−191 (*c* 1.120, 21)	3413, 3057, 2973, 1747, 1458, 1371, 1220, 1032, 744	607	Calcd for $C_{32}H_{34}N_2O_{10}$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.26; H, 5.55; N, 4.49
2	Pale brownish-white amorphous foam	+60.9 (*c* 1.005, 23)	3411, 3057, 2972, 1747, 1458, 1371, 1225, 1045, 746	607	Calcd for $C_{32}H_{34}N_2O_{10}$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.38; H, 5.48; N, 4.55
3	Pale brownish-white amorphous foam	−56.0 (*c* 1.050, 21)	3413, 3057, 2973, 1743, 1458, 1373, 1226, 1047, 744	607	Calcd for $C_{32}H_{34}N_2O_{10}$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.49; H, 5.68; N, 4.56
4	White amorphous foam	−11.8 (*c* 1.050, 21)	3411, 3053, 2974, 1747, 1458, 1371, 1225, 1045, 746	549	Calcd for $C_{30}H_{32}N_2O_8$: C, 65.68; H, 5.88; N, 5.11. Found: C, 65.39; H, 5.99; N, 4.92
5	White amorphous foam	+215 (*c* 1.000, 23)	3411, 3057, 2966, 1747, 1458, 1373, 1221, 1030, 744	535	Calcd for $C_{29}H_{30}N_2O_8$: C, 65.16; H, 5.66; N, 5.24. Found: C, 65.27; H, 5.51; N, 5.18
6	White amorphous foam	−216 (*c* 1.040, 23)	3411, 3057, 2929, 1747, 1458, 1371, 1223, 1030, 744	535	Calcd for $C_{29}H_{30}N_2O_8$: C, 65.16; H, 5.66; N, 5.24. Found: C, 65.18; H, 5.59; N, 5.17
7	White powder	−146 (*c* 1.045, 21)	3408, 3059, 2954, 1739, 1458, 1369, 1223, 1034, 752	534	Calcd for $C_{29}H_{30}N_2O_8$: C, 65.16; H, 5.66; N, 5.24. Found: C, 65.39; H, 6.02; N, 5.20
8	White powder	−57.5 (*c* 1.085, 23)	3419, 3057, 2979, 1747, 1458, 1371, 1225, 1047, 746	895	Calcd for $C_{44}H_{50}N_2O_{18}$: C, 59.05; H, 5.63; N, 3.13. Found: C, 58.97; H, 5.99; N, 3.03
9	White amorphous foam	−28.2 (*c* 1.120, 20)	3421, 3057, 2966, 1749, 1458, 1371, 1228, 1041, 746	895	Calcd for $C_{44}H_{50}N_2O_{18}$: C, 59.05; H, 5.63; N, 3.13. Found: C, 58.70; H, 5.80; N, 2.96
10	White amorphous foam	+21.2 (*c* 0.725, 21)	3421, 3057, 2962, 1747, 1458, 1371, 1232, 1041, 746	1183	Calcd for $C_{56}H_{66}N_2O_{26}$: C, 56.85; H, 5.62; N, 2.37. Found: C, 56.89; H, 5.70; N, 2.29

Table 3. Chemical shifts of compounds **1**–**7**

Compound no.	Chemical shifts δ (ppm)															
	Sugar moiety									Indole moiety						
	H-1	H-2	H-3	H-4	H-5a	H-5b	H-6a	H-6b	OAc	NH	H-2,2′	H-4,4′	H-5,5′	H-6,6′	H-7,7′
1	4.62	6.00	5.38	5.30	5.21		4.20	3.75	1.41, 1.88, 1.96, 1.98, 2.15	7.95 8.18	6.90 7.06	7.21 7.33	7.10 7.12	7.14 7.18	7.70 7.91
2	5.06	6.03	5.30	5.70	4.96		4.08	4.04	1.62, 1.63, 1.84, 2.02, 2.18	7.94 8.16	6.93 7.10	7.31	7.09 7.12	7.17 7.24	7.77 7.81
3	5.01	6.05	5.40	5.68	5.48		4.36	4.11	1.70, 1.89, 1.92, 2.00, 2.03	7.89 8.11	6.91 7.33	7.23 7.30	7.04 7.10	7.12 7.14	7.60 7.80
4	4.52	2.41 2.53	5.27	5.34	5.09		4.12	4.06	1.86, 1.99, 2.00, 2.09	7.98	7.03 7.11	7.31	7.02 7.04	7.13 7.15	7.56 7.59
5	4.75	6.08	5.35	5.15	4.19	4.00			1.49, 1.89, 1.97, 2.12	7.95 8.18	6.87 7.02	7.18 7.27	7.06 7.11	7.12	7.73 7.77
6	4.75	6.07	5.35	5.15	4.19	4.00			1.49, 1.88, 1.97, 2.12	7.97 8.21	6.85 7.00	7.15 7.26	7.06 7.12	7.12 7.17	7.73 7.77
7	4.78	6.02	5.42	5.21	4.21	3.96			1.55, 1.61, 1.94, 2.15	7.95 8.20	6.92 7.07	7.17 7.19	7.04 7.12	7.12	7.71 7.78

Table 4. Chemical shifts of compounds **8**, **9**, and **10**

Proton no.	**8**	**9**	**10**
H-1	5.00	4.82	4.81
H-2	6.15	6.05	6.04
H-3	5.34	5.41	5.42
H-4	4.17	4.00	3.99
H-5	5.02	5.27	5.26
H-6a	4.18	4.22	4.23
H-6b	3.95	4.10	4.10
H-1′	4.69	5.25	5.14
H-2′	5.19	4.90	4.78
H-3′	5.00	5.38	5.42
H-4′	5.36	5.08	3.93
H-5′	3.91	4.15	4.25
H-6′a	4.02	4.31	4.43
H-6′b	4.04	4.01	4.03
H-1″			5.42
H-2″			4.87
H-3″			5.36
H-4″			5.07
H-5″			3.95
H-6″a			4.23
H-6″b			4.10
OAc	1.62, 1.85, 1.87, 1.88, 1.98, 2.01, 2.07, 2.18	1.52, 1.91, 1.92, 1.95, 2.046, 2.053, 2.078, 2.082	1.52, 1.91, 1.92, 1.94, 2.00, 2.02, 2.03, 2.05, 2.09, 2.11
NH	8.09/8.11	8.08/8.30	8.10/8.35
H-2,2′	7.08/7.20	7.02/7.28	6.99/7.25
H-4,4′	7.31/7.32	7.30/7.35	7.27/7.33
H-5,5′	7.04/7.11	7.06/7.13	7.04/7.10
H-6,6′	7.14/7.16	7.15/7.17	7.14
H-7,7′	7.72/7.75	7.68/7.70	7.67/7.68

Table 5. Coupling constants of compounds **1**–**7**

Compound no.	Coupling constants (Hz)																
	$J_{1,2a}$	$J_{1,2b}$	$J_{2a,b}$	$J_{2a,3}$	$J_{2b,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,b}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,b}$	$J_{NH,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{4,6}$	$J_{5,7}$
1	10.2			1.6		9.7	2.2			7.3	4.7	11.7	2.4	8.1	8.1	8.1		
2	9.8			5.1		1.7	8.9			4.7	2.6	12.6	2.1	7.8	7.8	7.8	1.3	1.3
3	9.8			4.3		5.2	3.9			2.9	7.8	12.2	2.2	8.0	8.0	8.0	1.0	1.0
4	7.5	7.5	14.5	7.5	5.5	3.0	8.1			2.6	5.1	12.3		8.0	8.0	8.0	2.1	2.1
5	10.0			2.4		7.9	3.0	6.5	12.3				2.4	7.8	7.8	7.8		
6	10.0			2.5		7.8	3.0	6.5	12.4				2.1	8.1	8.1	8.1		
7	8.8			3.7		6.6	3.4	5.5	12.4				2.4	7.8	7.8	7.8		

reaction with a trisaccharide, maltotriose, was examined. The reaction proceeded smoothly, and the corresponding alditol was produced as the sole product in 36% yield. Since the H-4 and H-4′ NMR signals were observed at 3.99 and 3.93 ppm, respectively, the reaction appears to proceed regioselectively at the reducing terminus of maltotriose without cleavage of the two α-glycosidic bonds.

The reaction of two indoles with an unprotected sugar proceeded regioselectively at the reducing terminus of the sugar under these mild, simple, and environmentally benign reaction conditions, affording the 1-deoxy-1,1-bis(3-indoyl)alditol, without cleavage of O-glycosidic bonds in both di- and trisaccharides, in moderate to good yields. From the above results, the application of this reaction to other compounds having a high nucleophilicity, such as the 3-position of indole with unprotected oligosaccharides, to produce biologically active compounds should be possible.

1. Experimental

The solvents used in this reaction were all purified by distillation. $Sc(OTf)_3$ was purchased from Taiheiyo Kinzoku Co. Ltd. (Japan) and used without any further purification. For separation and purification, flash-column chromatography was performed using silica gel (230–400 mesh, Fuji-Silysia Co. Ltd., BW-300). Optical rotations were recorded on a JASCO DIP-370 polarimeter. IR measurements were achieved using a Horiba FT-720 IR spectrometer. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as the internal standard. Mass spectra were obtained by the fast-atom bombardment (FAB) method using 3-nitrobenzyl alcohol (NBA) as a matrix on a JEOL JMS-AX505HA instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument.

1.1. General procedure

Indole (163 mg, 1.39 mmol), D-galactose (100 mg, 0.555 mmol), and $Sc(OTf)_3$ (18.6 mg, 0.0278 mmol) were dissolved in 1 mL of 1:1 EtOH–water. The solution was then stirred at 50 °C for 2 days. After cooling to room temperature and adding sodium phosphate (5.7 mg, 0.04 mmol), the reaction mixture was evaporated in vacuo. The residue was dissolved in 5 mL of pyridine, and 5 mL of Ac_2O and DMAP (20 mg) were added to the solution. The solution was stirred at room temperature overnight. The reaction mixture was poured into 50 mL of ice-cold water and stirred for 30 min. The resulting precipitate was extracted twice with 10 mL of AcOEt. The combined extracts were washed with water and brine and dried over anhyd Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column

Table 6. Coupling constants (Hz) of compounds **8**, **9**, and **10**

Compound no.																					Indole moiety				
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,b}$	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,b}$	$J_{1'',2''}$	$J_{2'',3''}$	$J_{3'',4''}$	$J_{4'',5''}$	$J_{5'',6''a}$	$J_{5'',6''b}$	$J_{6''a,b}$	$J_{NH,2}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{4,6}$	$J_{5,7}$
8	7.0	5.1	5.1	5.1	2.9	6.7	12.3	7.9	10.3	3.4	1.0	6.5	7.2	11.3								2.0	7.8	7.8	7.8	1.0	1.0
9	9.3	1.8	7.0	7.0	3.4	7.6	12.1	3.9	10.2	10.0	10.0	4.3	2.0	12.3								2.4	7.8	7.8	7.8	~0	~0
10	9.4	2.0	3.2	—	3.4	6.8	—	3.8	9.8	—	—	2.6	2.3	12.5	4.0	9.8	9.8	9.8	—	—	—	2.3	7.9	7.9	7.9	1.0	1.0

Table 7. ^{13}C NMR chemical shifts of compounds **1**–**10**

Compound no.	Sugar moiety	Indole moiety
1	72.46, 68.77, 68.32, 67.93, 62.27, 34.97	136.70, 135.74, 127.58, 126.42, 123.68, 123.32, 121.95, 121.64, 120.00, 119.43, 119.34, 119.15, 115.24, 114.06, 111.59, 111.14
2	74.78, 69.84, 67.91, 66.85, 61.58, 34.28	135.99, 135.92, 127.34, 126.52, 122.37 (×2), 122.12, 121.63, 119.57, 119.36, 119.21, 119.12, 116.33, 114.55, 111.20 (×2)
3	74.53, 71.71, 70.83, 69.47, 62.03, 34.74	136.34, 135.94, 127.43, 126.49, 122.69, 122.56, 122.04, 121.65, 119.35, 119.22 (×2), 119.17, 115.76, 114.15, 111.36, 111.14
4	70.46, 70.02, 68.55, 61.90, 36.39, 30.53	136.77, 136.49, 126.87, 126.36, 122.40, 121.88, 121.78, 121.75, 119.69, 119.25, 119.20, 119.11, 118.46, 118.38, 111.28, 111.14
5	73.12, 70.14, 69.12, 62.34, 34.68	136.53, 135.80, 127.47, 126.31, 123.39, 122.70, 122.02, 121.62, 119.45, 119.42, 119.26, 119.08, 115.29, 114.07, 111.62, 111.19
6	73.06, 70.17, 69.14, 62.38, 34.75	136.59, 135.85, 127.55, 126.40, 123.39, 122.71, 122.07, 121.68, 119.56, 119.47, 119.33, 119.36, 115.41, 114.02, 111.59, 111.16
7	73.18, 70.94, 70.40, 62.20, 35.48	136.76, 135.94, 127.70, 126.49, 123.32 (×2), 122.24, 122.03, 119.84 (×2), 119.50 (×2), 114.96, 114.68, 111.55, 111.14
8	101.05, 76.53, 73.46, 71.17, 71.08, 70.99, 70.86, 69.07, 66.93, 61.33, 34.65	136.58, 135.76, 127.74, 126.53, 123.78, 122.82, 122.08, 121.83, 119.93, 119.35 (×2), 119.06, 115.33, 111.25, 111.11
9	96.70, 76.63, 74.12, 71.79, 71.34, 70.61, 69.92, 68.02 (×2), 61.68, 61.60, 34.84	136.89, 135.56, 127.58, 126.51, 123.79, 122.97, 121.99, 121.57, 119.39, 119.34, 119.09, 119.06, 115.06, 114.08, 111.56, 111 29
10	97.04, 95.60, 77.26, 73.79, 72.63, 72.15, 71.82, 71.31, 70.94, 70.05, 69.37, 68.63, 68.47, 67.98, 62.49, 61.80, 61.40, 35.01	136.86, 135.50, 127.66, 126.68, 123.69, 122.96, 122.08, 121.70, 119.52, 119.47, 119.24, 119.17, 115.28, 114.41 (×2), 111.16

chromatography on silica gel (2:1 hexane–AcOEt) to give **1** (290.2 mg, 86.3%) as a pale brownish-white amorphous foam.

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