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Total Synthesis of the Proposed Structure of Indolyl 1,2-Propanediol Alkaloid, 1-(1*H*-Indol-3-yloxy)propan-2-ol

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Abstract: The first total synthesis of the proposed structure of unprecedented indolyl derivative bearing 1,2-propanediol moiety is described. Isomerization of 3-alkoxyindolines through indolenium intermediates was the key step in the total synthesis. ^{1}H, ^{13}C-NMR, IR, and HRMS spectra of the synthetic compound drastically differed to those of the originally reported structure, which suggests the natural product requires revision.

Keywords: 1-(1*H*-indol-3-yloxy)propan-2-ol; indole alkaloid; isomerization; silver; umpolung

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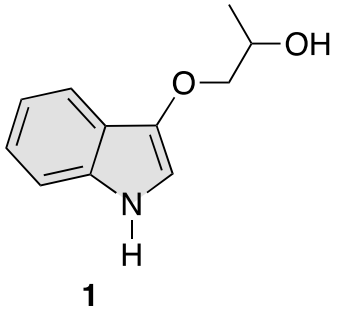
1. Introduction

Alkoxyindoles are privileged structures that are found in natural products, which exhibit significant biological activities and are interesting targets for organic chemistry [1]. For example, koniamborine, isolated from *Boronnella koniambiensis* aerial parts, shows significant cytotoxicity against the L1210 cancer cell line [2]. Cladoniamide G, isolated from cultures of *Streptomyces uncialis*, is also cytotoxic to MCF-7 cells in vitro at 10 mg/mL [3]. Pyrrolidinoindoline-type alkaloid CPC-1 was isolated from the seeds and rinds of *Chimonanthus praecox* f. concolor [4]. Oxytrofalcatins A-F and 3-oxygenated N-benzoyl indole analogs from the roots of *Oxytropis falcata* (Leguminosae) were revised to 2,5-diaryloxazoles by Abe and Yamada [5,6]. Isolated natural products represent a valuable resource of pharmaceutical reagents [7], such as the 5-HT$_4$ antagonist [8], antiproliferative agents [9], and VATPase inhibitors [10]. Therefore, developing concise routes for oxygenated indoles is of great significance. Although there are indirect methods to access such oxygenated indoles [11–18], many efforts have been made toward direct oxy-functionalization at C2 or C3 positions in indolines or indoles [19–22]. In 2000, Kettle and coworkers reported that rhodium(II)-catalyzed O–H insertion reactions of 2-carboethoxy-3-diazo-3H-indole to generate high 3-alkoxyindole yields [23]. Zhang's group presented a direct approach to C3-acetoxylated biindolyls via palladium catalysis using AgOAc under oxygen atmosphere as oxidants [24]. In contrast to the vast majority of metal-catalyzed synthesis approaches for oxygenated indoles [25–35], metal-free approaches have emerged as powerful synthetic tools owing to their sustainable properties [36–47]. However, these reactions are limited to the construction of either C2-oxygenated or C3-oxygenated indole/indoline. Given the difficulty of switchable construction for oxygenated indole/indoline, we recently reported the regioselective synthesis of both 2- and 3-alkoxyindoles from the common intermediate, 2-alkoxy-3-bromoindolines (ROBIN) [48]. The synthesis of 2-alkoxyindoles was achieved by a base-mediated regioselective elimination of HBr from ROBIN. In other hands, 3-alkoxyindoles were obtained by silver-mediated alkoxylation followed by the BF_3•OEt_2-promoted elimination of alkoxide at the C3-position of the indole ring.

1-(1*H*-Indol-3-yloxy)propan-2-ol (**1**) is an indolyl derivative isolated from the Red Sea sponge *Haliclona* sp. and was published in 2016 by Al-Massarani and co-workers (Figure 1) [49]. Structurally, 1-(1*H*-Indol-3-yloxy)propan-2-ol (**1**) differs from previously reported alkoxyindoles [1–9]. It has an unprecedented 1,2-propandiol moiety at the C3

position of indole. Furthermore, 1,2-propandiol possesses anti-microbial activity, and is used as a preservative agent in pharmaceuticals and food [50].



1

Figure 1. Proposed structure of 1-(1*H*-Indol-3-yloxy)propan-2-ol (**1**) as the first indolyl 1,2-propandiol alkaloid.

Potential biological activity in combination with unprecedented indolyl saccharide bearing 1,2-propandiol makes 1-(1*H*-indol-3-yloxy)propan-2-ol (**1**) an attractive synthetic target for medicinal and synthetic chemistry. However, the structure of **1** was determined by 2D-NMR and MS analyses, while neither of its [α]D data nor absolute configurations were presented. Furthermore, the reported ^{1}H-NMR spectrum of **1** in CD_3OD showed a resonance at 7.95 ppm (H-2), which was too low a field shift for 3-alkoxyindoles. These inconsistencies suggest that organic synthesis is needed to confirm the structure, including the absolute configuration of **1**. Based on our interest in 3-alkoxyindoles, the determination of the real **1** structure is worth investigating. Herein, we report the total synthesis of the proposed structure of **1** starting from *N*-tosylindole (**2**).

2. Materials and Methods

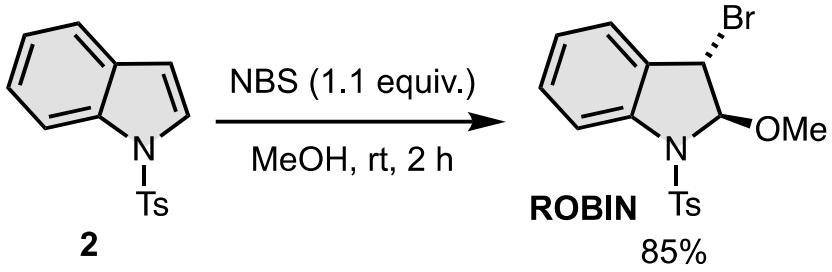
High-resolution MS spectra were recorded with a Brucker micrOTOF mass spectrometers (ESI-TOF-MS). NMR experiments were performed with a JEOL JNM-ECZ600R (^{1}H NMR: 600 MHz, ^{13}C NMR: 151 MHz) spectrometer, a Varian 600-MR ASW (^{1}H NMR: 600 MHz, ^{13}C NMR: 151 MHz) spectrometer, and a Varian 400-MR ASW (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) spectrometer, with chemical shifts expressed in ppm (δ) using residual undeuterated solvent as an internal reference. ^{1}H NMR spectra were referenced to tetramethylsilane as an internal standard or to a solvent signal ($CDCl_3$: 7.26 ppm, methanol-d_6: 3.31 ppm, DMSO-d_6: 2.50 ppm). ^{13}C NMR spectra were referenced to a solvent signal ($CDCl_3$: 77.1 ppm, methanol-d_6: 49.00 ppm, DMSO-d_6: 39.52 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, br = broad; coupling constants in Hz; integration. Reactions were monitored by thin layer chromatography (TLC) carried out on a silica gel plates (60F-254) and visualized under UV illumination at 254 or 365 nm depending on compounds. Flash column chromatography was performed on silica gel (WAKO Gel 75–150 mesh, WAKO Co., Ltd., Tokyo, Japan). All substrates were used as received from commercial suppliers (Sigma-Aldrich, Tokyo, Japan; Kanto Chemical, Tokyo, Japan; TCI, Tokyo, Japan; and Wako, Tokyo, Japan) and all reagents were weighed and handled in air at room temperature. All work-up and purification steps were carried out with reagent-grade solvents in air.

*2.1. Synthesis of N-Tosylindoles (**2**) [51]: N-Tosylindoles (**2**) Was Prepared by a Reported Method [50]*

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (ddd, *J* = 8.3, 1.8, 1.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 3.6 Hz, 1H), 7.53 (ddd, *J* = 7.7, 1.2, 0.8 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.23 (ddd, *J* = 7.6, 6.8, 1.2 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.66 (dd, *J* = 3.6, 0.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.9, 135.3, 134.8, 130.7, 129.8, 126.8, 126.3, 124.5, 123.2, 121.3, 113.5, 109.0, 21.5.

2.2. Synthesis of Trans-3-Bromo-2-methoxy-1-tosylindoline (ROBIN) [48]

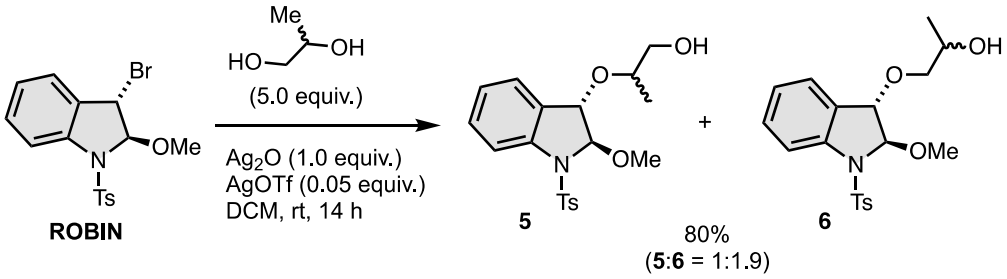
To generate a solution of **2** (2.71 g, 10 mmol) in MeOH (100 mL, 0.1 M), we added NBS (1.96 g, 11 mmol). The mixture was stirred at room temperature for 2 h. After filtration, ROBIN was obtained as a crystal; 3.26 g, 85% yield; White crystal; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.34 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.28 (ddd, *J* = 7.8, 1.4, 0.8 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.11 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 5.59 (s, 1H), 4.95 (s, 1H), 3.61 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.5, 140.5, 135.1, 131.3, 130.5, 129.5, 127.7, 126.1, 125.3, 116.9, 99.8, 56.3, 47.1, 21.5.



Analytical data are in accordance with literature values.

2.3. Synthesis of **5** *and* **6**

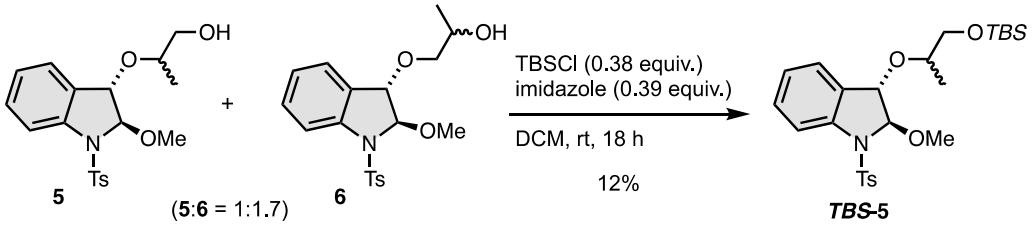
To a solution of ROBIN (3.82 g, 10 mmol), propane-1,2-diol (3.7 mL, 50 mmol) in DCM (50 mL, 0.2 M) was added to Ag_2O (2.32 g, 10 mmol) and AgOTf (128.5 mg, 0.50 mmol). The mixture was stirred at room temperature for 14 h. After filtration and concentrated in vacuo, the residue was purified by silica gel column chromatography (AcOEt/hexane = 1/10–1/1) to generate a mixture of **5** and **6** (**5**:**6** = 1.0:1.9). 3.02 g, 80% yield; Orange oil.



Analytical samples **5** and **6** were obtained by TBS protection and separated by silica gel column chromatography.

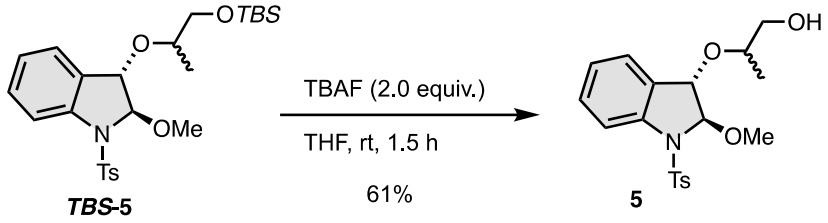
2.3.1. Synthesis of Trans-3-((1-*tert*-Butyldimethylsilyloxy)propan-2-yloxy)-2-methoxy-1-tosylindoline (***TBS*-5**)

To a solution of a mixture of **5** and **6** (3.33 g, 8.8 mmol, **5**:**6** = 1:1.7) and imidazole (236.5 mg, 3.5 mmol) in DCM (60 mL, 0.15 M), we added TBSCl (498.4 mg, 3.3 mmol). The mixture was stirred at room temperature for 18 h. After filtration, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate ***TBS*-5** (dr = 1.2:1). 523.7 mg, 12% yield; Yellow oil; IR (KBr): 1358, 1169, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.61–7.59 (m, 1H), 7.33–7.27 (m, 2H), 7.15–7.11 (m, 2H), 7.09–7.03 (m, 1H), 5.42 (s, 0.52H), 5.33 (s, 0.37 H), 4.73 (s, 0.41H), 4.58 (s, 0.48H), 3.72–3.64 (m, 1H), 3.601, 3.598 (2s, 3H), 3.52–3.28 (m, 2H), 2.32, 2.31 (2s, 3H), 1.04 (d, *J* = 7.2 Hz, 1.04H), 0.92 (d, *J* = 8.0 Hz, 1.53H), 0.94, 0.89 (2s, 9H), 0.11, 0.04, 0.03 (3s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 143.9, 143.8, 141.72, 141.65, 135.4, 135.3, 131.1, 130.9, 130.3, 130.2, 129.4, 129.3, 127.9, 127.6, 126.64, 126.60, 124.7, 124.6, 117.1, 116.9, 98.2, 97.8, 81.4, 81.2, 75.3, 74.9, 67.09, 67.05, 56.0, 55.9, 26.0, 25.9, 21.56, 21.54, 18.5, 18.3, 17.7, 17.2, −5.25, −5.27, −5.32, −5.42; HRMS (ESI) *m*/*z*: 514.2059 (Calcd for $C_{25}H_{37}NNaO_5SSi$ $[M + Na]^+$: 514.2059).



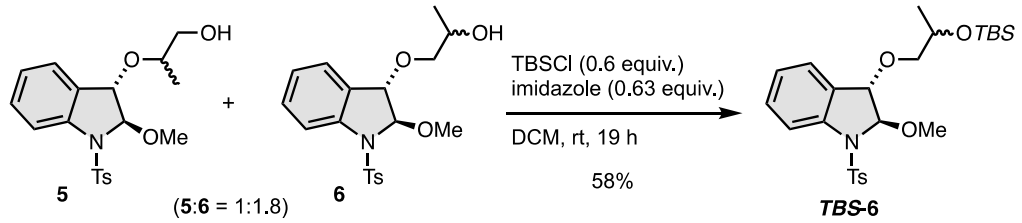
2.3.2. Synthesis of 2-(Trans-2-methoxy-1-tosylindolin-3-yloxy)propan-1-ol (**5**)

To a solution of ***TBS*-5** (267.0 mg, 0.54 mmol) in THF (3.6 mL, 0.15 M), we added TBAF in THF (1.1 mL, 1.1 mmol). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/1) to generate **5** (dr = 1.5:1). 124.7 mg, 61% yield; Yellow oil; IR (KBr): 1352, 1167, 1111, 1090, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (t, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.36 (tt, *J* = 8.0, 1.6 Hz, 1H), 7.27 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.18–7.16 (m, 2H), 7.13–7.08 (m, 1H), 5.31 (s, 0.6H), 5.26 (s, 0.38H), 4.53 (s, 0.57H), 4.47 (s, 0.37H), 3.78–3.63 (m, 1H), 3.60, 3.59 (2s, 3H), 3.45 (dd, *J* = 11.8, 3.6 Hz, 0.50H), 3.31–3.26 (m, 1H), 3.07 (dd, *J* = 11.6, 6.8 Hz, 0.39H), 2.34, 2.33 (2s, 3H), 1.11 (d, *J* = 6.0 Hz, 1.20H), 1.03 (d, *J* = 6.4 Hz, 1.90H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.4, 144.3, 141.8, 141.7, 135.3, 135.1, 131.0, 130.6, 130.5, 130.4, 129.5, 129.2, 127.5, 127.4, 126.5, 126.3, 125.0, 124.9, 117.7, 117.2, 98.2, 97.4, 80.7, 80.4, 74.84, 74.79, 66.1, 66.0, 56.04, 55.96, 21.5, 21.4, 16.0, 15.9; HRMS (ESI) *m*/*z*: 400.1195 (Calcd for $C_{19}H_{23}NNaO_5S$ [M + Na]$^+$: 400.1195).



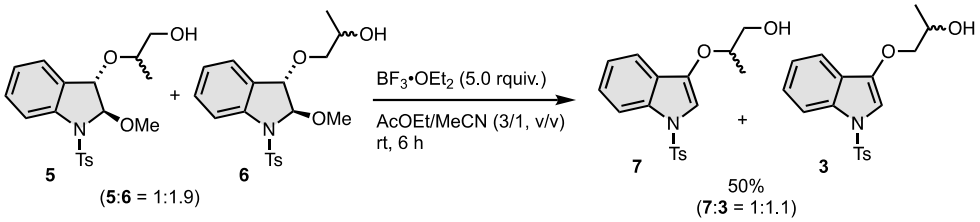
2.3.3. Synthesis of 1-(Trans-2-Methoxy-1-tosylindolin-3-yloxy)propan-2-ol (***TBS*-6**)

To a solution of a mixture of **5** and **6** (3.91 g, 10 mmol, **5**:**6** = 1:1.8) and imidazole (444.6 mg, 6.5 mmol) in DCM (65 mL, 0.15 M), we added TBSCl (937.4 mg, 6.2 mmol). The mixture was stirred at room temperature for 19 h. After filtration, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate ***TBS*-6** (dr = 1.3:1). 2.23 g, 58% yield; Yellow oil; IR (KBr): 1358, 1167, 1109, 1084, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 7.6 Hz 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 5.31, 5.29 (2s, 1H), 4.37 (s, 1H), 3.57 (s, 3H), 3.57–3.53 (m, 1H), 3.36 (dd, *J* = 8.8, 2.4 Hz, 0.54 H), 3.28 (dd, *J* = 8.6, 2.8 Hz, 0.42H), 3.21–3.15 (m, 1H), 0.99 (2d, *J* = 6.0, 4.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.3, 144.2, 141.83, 141.76, 135.23, 135.20, 130.57, 130.55, 130.2, 130.1, 129.35, 129.32, 127.41, 127.40, 126.71, 126.70, 124.79, 124.72, 117.46, 117.41, 96.9, 96.8, 82.9, 82.8, 74.3, 74.1, 66.14, 66.10, 55.9, 21.43, 21.41, 18.41, 18.38; HRMS (ESI) *m*/*z*: 400.1195 (Calcd for $C_{19}H_{23}NNaO_5S$ [M + Na]$^+$: 400.1195).



2.4. Synthesis of **7** *and* **3**

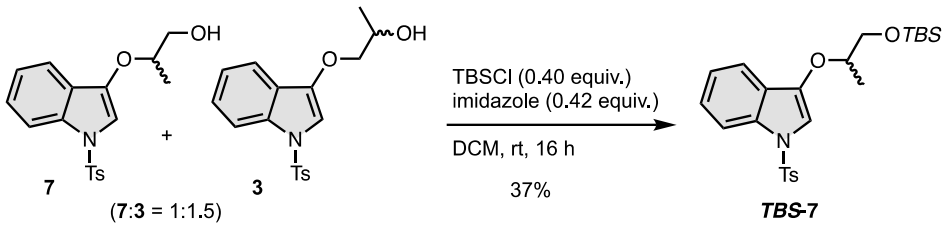
A mixture of **5** and **6** (113.2 mg, 0.30 mmol, **5**:**6** = 1:1.9) was dissolved in AcOEt/MeCN (3/1, 2.4 mL, 0.125 M). To this solution, we added $BF_3 \bullet Et_2O$ (0.19 mL, 1.5 mmol) and the mixture was stirred at room temperature for 6 h. After addition of H_2O, the mixture was extracted with AcOEt (3 × 10 mL) and washed with saturated $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate a mixture of **7** and **3** (**7**:**3** = 1:1.1). 52.1 mg, 50% yield; Yellow oil.



Analytical sample **7** was obtained by TBS protection and separated by silica gel column chromatography.

2.4.1. Synthesis of 3-((1-*tert*-Butyldimethylsilyloxy)propan-2-yloxy)-1-tosyl-1*H*-indole (**TBS-7**)

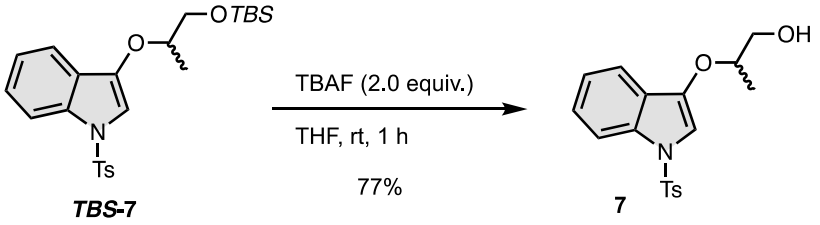
To a solution of a mixture of **7** and **3** (965.5 mg, 2.8 mmol, **7**:**3** = 1:1.5) and imidazole (81.7 mg, 1.2 mmol) in DCM (19 mL, 0.15 M), we added TBSCl (168.8 mg, 1.1 mmol). The mixture was stirred at room temperature for 16 h. After filtration, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate ***TBS*-7**. 415.2 mg, 37% yield; Orange oil; IR (KBr): 1367, 1215, 1174, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.99 (ddd, *J* = 8.0, 0.8, 0.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.50 (ddd, *J* = 7.8, 1.2, 0.8 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 4.26 (tq, *J* = 6.0, 2.8 Hz, 1H), 3.82 (dd, *J* =11.0, 5.6 Hz, 1H), 3.71 (dd, *J* = 10.6, 4.8 Hz, 1H), 2.32 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.06, 0.02, 0.00 (3s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ:144.7, 144.5, 134.3, 129.8, 126.9, 125.7, 123.3, 118.9, 114.3, 105.6, 78.1, 66.1, 26.0, 21.7, 16.3, 0.14, −5.13, −5.20; HRMS (ESI) *m*/*z*: 482.1797 (Calcd for $C_{24}H_{33}NNaO_4SSi$ [M + Na]$^+$: 482.1797).



2.4.2. Synthesis of 1-(1-Tosyl-1*H*-indol-3-yloxy)propan-2-ol (**7**)

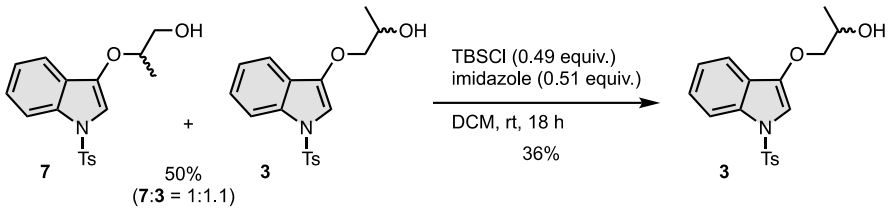
To a solution of ***TBS*-7** (415.2 mg, 1.1 mmol) in THF (7.0 mL, 0.15 M), we added TBAF in THF (2.1 mL, 2.1 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate 7. 279.4 mg, 77% yield; Yellow oil; IR (KBr): 1363, 1213, 1173, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.00 (ddd, *J* = 8.4, 0.8, 0.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.51 (ddd, *J* = 8.0, 1.2, 0.8 Hz, 1H), 7.33 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.97 (s, 1H), 4.36 (tq, *J* = 6.0, 3.6 Hz, 1H), 3.79 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.75 (dd, *J* = 12.0, 6.8 Hz, 1H), 2.31 (s, 3H), 1.32 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ:144.5, 143.6, 134.4, 133.8, 129.5, 126.5, 125.6,

125.1, 123.0, 118.3, 114.0, 105.8, 77.8, 65.8, 21.3, 15.2; HRMS (ESI) *m*/*z*: 368.0933 (Calcd for $C_{18}H_{19}NNaO_4S$ [M + Na]$^+$: 368.0933).



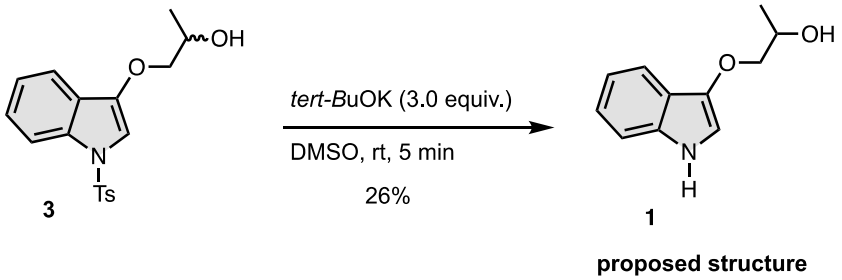
*2.5. Synthesis of 2-(1-Tosyl-1H-indol-3-yloxy)propan-1-ol (**3**)*

To a solution of a mixture of **7** and **3** (521.0 mg, 1.5 mmol, **7**:**3** = 1:1.1) and imidazole (52.9 mg, 0.77 mmol) in DCM (10 mL, 0.15 M), we added TBSCl (111.9 mg, 0.74 mmol). The mixture was stirred at room temperature for 18 h. After filtration, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate 3. 188.1 mg, 36% yield; Yellow oil; IR (KBr): 1362, 1215, 1173, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (ddd, *J* = 8.4, 0.8, 0.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.52 (ddd, *J* = 7.8, 1.6, 0.8 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.22 (ddd, *J* = 7.8, 7.2,1.2 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 4.26 (tq, *J* = 3.6, 3.2 Hz, 1H), 3.97 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.84 (dd, *J* = 9.4, 8.0 Hz, 1H), 2.32 (s, 3H), 1.31 (d, *J* = 6.8, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ:145.7, 145.2, 135.1, 134.5, 130.2, 127.2, 126.3, 124.9, 123.7, 118.9, 114.7, 105.1, 76.3, 66.6, 22.0, 19.2; HRMS (ESI) *m*/*z*: 368.0933 (Calcd for $C_{18}H_{19}NNaO_4S$ [M + Na]$^+$: 368.0933).



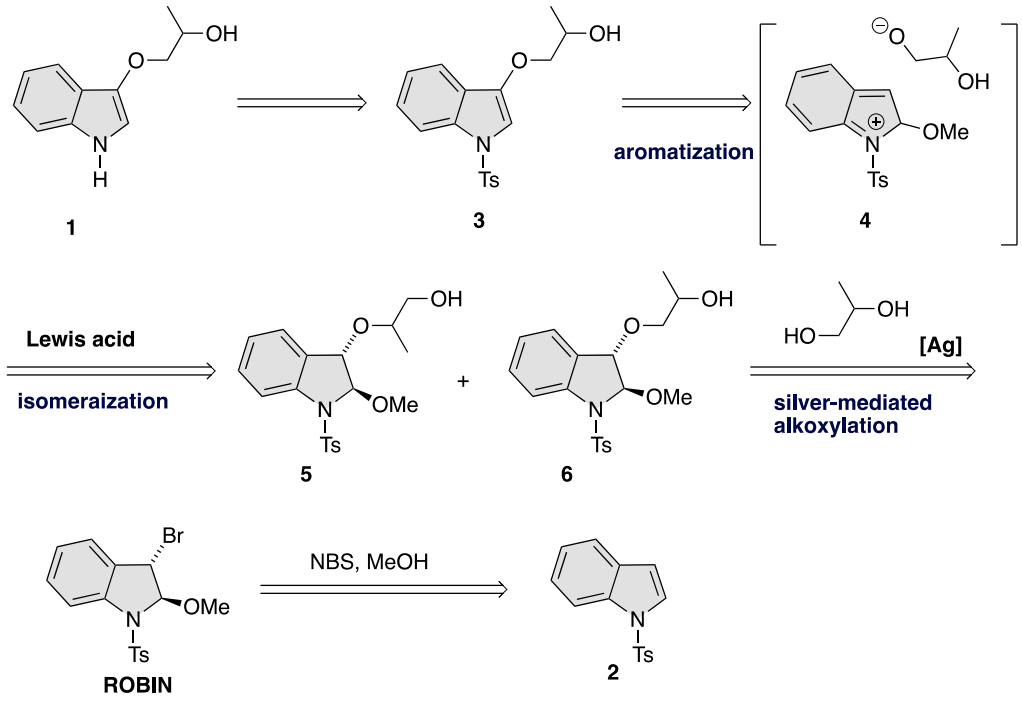
*2.6. Synthesis of 1-(1H-Indol-3-yloxy)propan-2-ol (**1**)*

To solution **3** (283.2 mg, 0.82 mmol) in DMSO (8.2 mL, 0.1 M), we added *t*BuOK (276.0 mg, 3.0 equiv.). The mixture was stirred at room temperature until the complete disappearance of starting material, as indicated by TLC. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with AcOEt (3 × 10 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5–1/1) to generate **1**. 40.2 mg, 26% yield. yellow oil. IR (KBr): 3419, 1558, 1234, 1101 cm^{-1}; ^{1}H NMR (600 MHz, Methanol-d_4) δ: 7.57 (ddd, *J* = 7.8, 1.2, 1.2 Hz, 1H), 7.25 (ddd, *J* = 8.4, 0.6, 0.6 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 6.80 (s, 1H), 4.17 (tq, *J* = 6.0, 5.4 Hz, 1H), 3.90 (dd, *J* = 5.7, 0.6 Hz, 2H), 1.30 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, Methanol-d_4) δ: 140.1, 134.5, 121.6, 119.4, 117.7, 117.1, 110.9, 105.5, 76.2, 65.9, 18.4; HRMS (ESI) *m*/*z*: 214.0844 (Calcd for $C_{11}H_{13}NNaO_2$ [M + Na]$^+$: 214.0844).



3. Results and Discussion

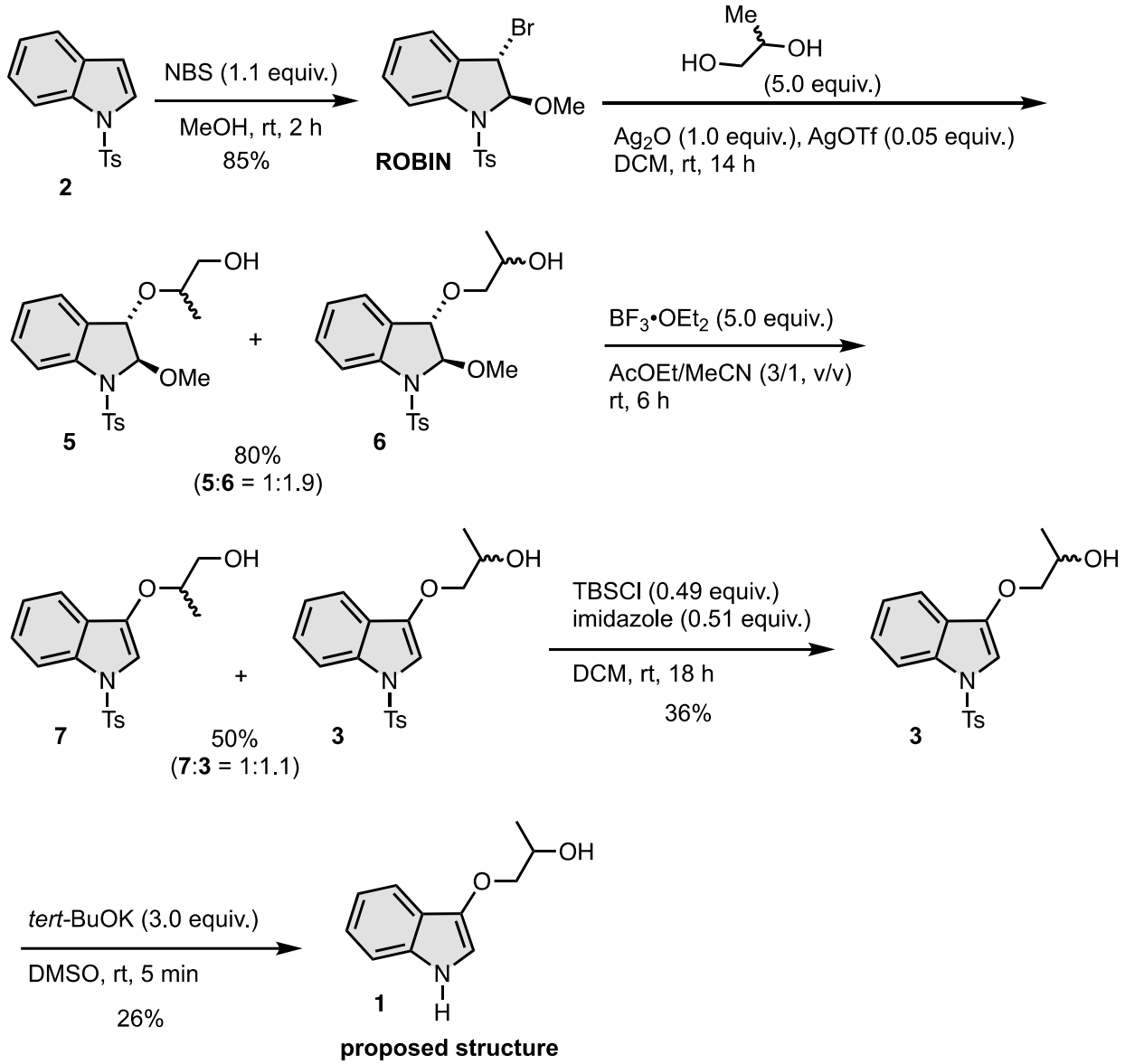
Our retrosynthesis of **1** was based on a convergent process involving the Lewis acid-mediation of 3-alkoxyindoles **5** and **6** isomerization through an indolenium intermediate **4** as a key step (Scheme 1). Thus, the hydroxy group serves as a handle to direct isomerization reactions in a regioselective manner. The isomerization precursors **5** and **6** are obtained from 3-bromo-2-methoxyindole (ROBIN: 2-RO-3-bromoindoline) through silver-mediated alkoxylation. ROBIN is synthesized through the bromoetherification of a commercially available *N*-tosylindole (**2**) using NBS (*N*-bromosuccinimide) in MeOH [52].



Scheme 1. Our retrosynthetic analysis for **1**.

Synthesis commenced from N-tosylindole (**2**) (Scheme 2). According to our previously developed protocol [48], ROBIN (2-RO-3-bromoindoline) was obtained in high yields. Next, silver-mediated alkoxylation of ROBIN with 1,2-propandiol as a nucleophile was conducted, generating desired alkoxyindoles **5** and **6** as a regioisomeric mixture (1.0:1.9) at an 80% yield. We observed that the regioisomeric ratio (**5**:**6**) ranged from 1.0:1.9 to 1.0:1.7 (See, Sections 2, 2.3.1 and 2.3.3). This result suggested that the alkoxylation might be a reversible reaction, probably through possible intermediates such as a spiroketal intermediate [53,54] or an indolenium ion [55]. From the regioisomeric ratio (**5**:**6**), it was assumed that the isomerization step preferred a less-steric hindered nucleophilic attack by the 1° alcohol to steric-hindered nucleophilic attack by the 2° alcohol. To our knowledge, the isomerization of 3-alkoxyindoles has not been previously reported. Unfortunately, alkoxyindoles **5** and **6** could not be directly separated by preparative TLC and silica gel column chromatography. Thus, analytical samples of **5** and **6** were obtained after *tert*-butyldimethylsilyl (TBS) protection/separation by silica gel column chromatography (See, Section 2). The mixture of **5** and **6** was evaluated in a demethoxylative aromatization reaction without further purification. An initial screen of Brønsted acids resulted in decomposition, probably due to the presence of free alcohol. After intensive screening of Brønsted and Lewis acids (BF_3•OEt_2, $AlCl_3$, $ZnCl_2$, $FeCl_2$, $InCl_3$, $InBr_3$, $In(OTf)_3$, and $Yb(OTf)_3$), we observed that BF_3•OEt_2 in AcOEt/MeCN generated the desired alkoxyindole **7** and **3** as a regioisomeric mixture (1.0:1.1) at a 50% yield [50]. The change in the diastereomeric ratio from 1.0:1.9 (**5**:**6**) to 1.0:1.1 (**7**:**3**) suggested that the demethoxylative aromatization of **5** and **6** occurred through cyclic intermediates such as a spiroketal intermediate **4′**, which permitted the

reaction through a stabilized oxonium ion. If the reaction proceeded as an acyclic intermediate [54], a less-steric hindered alkoxy exchange would be preferred. The undesired regioisomer **7** became separable after performing TBS protection/separation by silica gel column chromatography using 0.49 equiv. of TBSCl and 0.51 equiv. of imidazole to generate the secondary alcohol **3**.

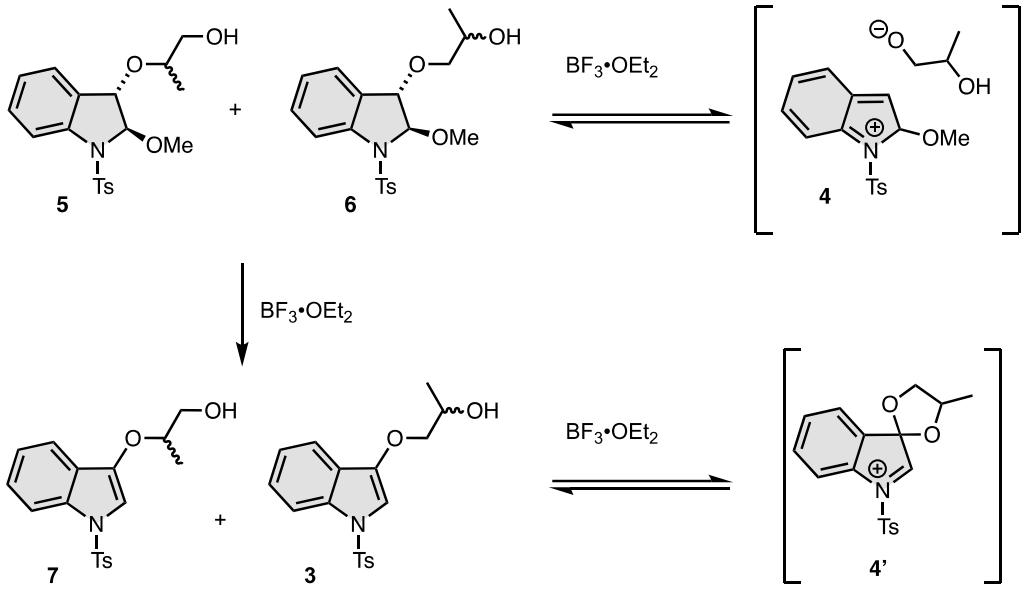


Scheme 2. Synthesis of proposed structure **1**.

Next, we performed the detosylation of **3** to obtain N–H compound **1**. Using NaOH-mediated detosylation, a trace amount of the desired N–H compound **1** was obtained due to its instability. In general, **1** displayed valuable stability to reaction conditions, which allowed us to determine more mild conditions. After intensive investigations, we found that *tert*-BuOK, which is a known steric hindered base, generated acceptable yields of the proposed structure **1** [56]. It was noteworthy that this detosylation tolerated the presence of free OH in **3**.

The plausible mechanism of the isomerization of the mixture **5** and **6** is shown in Scheme 3. First, BF_3•OEt_2 promoted the elimination of an alcohol moiety (1,2-propandiol) which generated the common intermediate **4**. Then, alkoxylation/demethoxylative aromatization occurred in the presence of 5 equivalents of BF_3•OEt_2 to generate the mixture **7**

and **3** with the ratio of 1.0:1.1. This reaction proceeded through the intermediate **4′** due to an increase in the formation of sterically hindered **5**.

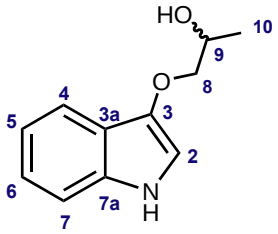


Scheme 3. Plausible isomerization mechanism.

The structure of 1-(1*H*-Indol-3-yloxy)propan-2-ol isolated from the Red Sea sponge *Haliclona* sp. was determined using NMR and HRMS data (Supplementary Material). A comparison of synthetic sample **1** ^{1}H and ^{13}C NMR spectra with the literature revealed significant differences [49].

The largest ^{1}H chemical shift differences were found for H2 (Table 1, synthetic **1**: 6.80 ppm vs. reported **1**: 7.95 ppm). The aromatic benzene region of the ^{1}H chemical shift of our synthetic **1** was also different from reported **1** (synthetic **1**: 6.95, 7.08, 7.25, and 7.57 ppm vs. reported **1**: 7.16, 7.20, 7.45, and 8.13 ppm). Large ^{13}C chemical shift differences were also observed for C2, C3, and C3a positions (Table 2, synthetic **1** (C2): 105.5 ppm vs. reported **1** (C2): 133.6 ppm; synthetic **1** (C3): 119.4 ppm vs. reported **1** (C3): 110.0 ppm; synthetic **1** (C3a): 140.1 ppm vs. reported **1** (C3a): 128.0 ppm). These key discrepancies in ^{1}H and ^{13}C NMR data potentially suggested an incorrectly determined indole ring system [6,57]. Unsurprisingly, misinterpretation of ^{1}H and ^{13}C NMR data is the most common reason for the misassignment of natural products [58–64]. To our surprise, we found that High-Resolution Mass Spectrometer (HRMS) data were also different (synthetic **1** vs. reported **1**). In the isolation paper of **1**, authors commented "Its high-resolution electron impact mass spectrometry (HREI-MS) showed an odd molecular ion peak at *m*/*z* 191.0946". Molecular formula assignment is one of the critical steps in assigning a structure to an isolated natural product, and is based on matching isotopic composition to detected *m*/*z* values [65]. However, assignment can be interfered with by the complicated nature of peaks containing heteroatoms along with peaks containing heavy isotopes. Based on HRMS data differences between synthetic **1** [HRMS (ESI) *m*/*z*: 214.0844 (Calcd for $C_{11}H_{13}NNaO_2$ $[M + Na]^+$)] and reported **1** [HRMS (ESI) *m*/*z*: 191.0946 (Calcd for $C_{11}H_{13}NO_2$ $[M]^+$], a wrong heteroatom assignment might also occur [66]. Therefore, we suggest that the indolyl 1,2-propanediol alkaloid may be another heterocyclic compound.

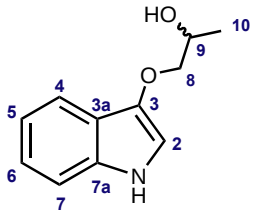
Table 1. ^{1}H-NMR data comparisons between synthetic and natural **1** samples.



1

Position	Synthetic 1 δ_H (mult, *J* in Hz) 600 MHz, methanol-d_4	Natural 1 δ_H (mult, *J* in Hz) 500 MHz, methanol-d_4
2	6.80 (s)	7.95 (br s)
4	7.57 (ddd, 7.8, 1.2, 1.2)	8.13 (br d, 7.8)
5	6.95 (ddd, 8.0, 7.2, 1.2)	7.16 (dt, 7.6, 1.3)
6	7.08 (ddd, 8.1, 7.2, 1.2)	7.20 (dt, 7.6, 1.3)
7	7.25 (ddd, 8.4, 0.6, 0.6)	7.45 (br d, 7.6)
8	3.90 (dd, 5.7, 0.6)	3.44 (m)
9	4.17 (tq, 6.0, 5.4)	3.80 (m)
10	1.30 (d, 6.0)	1.15 (d, 6.4)

Table 2. ^{13}C-NMR data comparisons between synthetic and natural **1** samples.



1

Position	Synthetic 1 δ_C 151 MHz, methanol-d_4	Natural 1 δ_C 125 MHz, methanol-d_4
2	105.5	133.6
3	119.4	110.0
3a	140.1	128.0
4	117.1	122.2
5	117.7	122.1
6	121.6	123.4
7	110.9	112.8
7a	134.5	138.2
8	76.2	68.5
9	65.9	69.2
10	18.4	19.6

4. Conclusions

We accomplished the first total synthesis of the proposed structure of an unprecedented indolyl saccharide alkaloid **1** bearing a 1,2-propandiol moiety. Isomerization of 3-alkoxyindolines through indolenium intermediates were key steps in the total synthesis. Our synthetic route was concise, requiring only five steps from N-Ts indole and yielding the target **1** at a 3% overall yield. ^{1}H, ^{13}C-NMR, IR, and HRMS spectra of the synthetic compound drastically differed to originally reported structure spectra. In the organic chemistry field, structural misassignments are problematic [66] and may be avoided using NMR chemical shift calculations [67] or machine learning [68,69]. A difficult task is to find

the correct revision in the first place. Further synthetic studies to revise the natural product are ongoing in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry5040177/s1. The Supplementary Materials contain analytical data including Figures S1–S14: ^{1}H- and ^{13}C-NMR spectra.

Author Contributions: Conceptualization, T.A.; investigation, T.A.; resources, T.A.; visualization, T.A.; structures, T.A.; experiments, M.K.; writing—original draft preparation, T.A.; writing—review and editing, T.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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