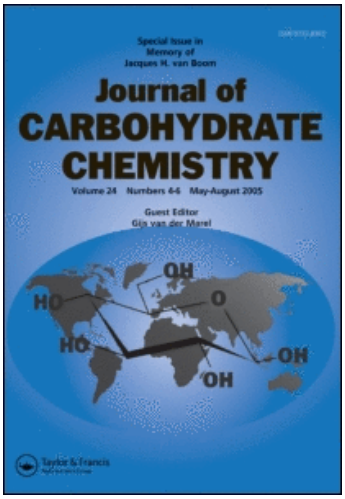

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Zhao Yu[a]; Lu Ya-Peng[a]; Zhu Li[a]
[a] Institute of Nautical Medicine, Nantong University, Nantong, Jiangsu, China

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Synthesis of Per-acetyl D-fucopyranosyl Bromide and Its Use in Preparation of Diphyllin D-fucopyranosyl Glycoside

Zhao Yu, Lu Ya-Peng, and Zhu Li

Institute of Nautical Medicine, Nantong University, Nantong, Jiangsu, China

The per-*O*-acetyl-D-fucosyl bromide (**9**) was expediently prepared for C-6 deoxygenation of D-galactose in six steps in 32.5% yield. Employing phase transfer catalysis glycosylation (PTC), D-fucopyranosyl diphyllin (**4**), the analog of natural diphyllin glycoside, was synthesized by using **9** as the glycosyl donor in 67.1% in two steps. The product was identified by ^{1}H NMR, ^{13}C NMR, and HRMS. Its abilities to inhibit the growth of cancer cells in vitro also are discussed.

Keywords D-galactoses, D-fucose, Synthesis, Glycosylation, Antitumor

INTRODUCTION

Diphyllin, an arylnaphthalene lignan isolated from many traditional medicinal plants, has been reported to possess a wide range of pharmacological activity, including antitumor and antiviral activities.[1–3] Interestingly, some natural diphyllin glycosides (**1**–**3**, Patentiflorin A, Patentiflorin B, and 4″-*O*-acetyl patentiflorin B) showed more potent bioactivities than aglycone diphyllin itself.[4–9] It has been proved that sugar moieties are crucial to their bioactivities and pharmacokinetics.[4] In order to ascertain the relationship between the stereochemical orientation of the C-4" hydroxyl group and biological activity, we set out to synthesize the β-D-fucosyl analog **4** of natural diphyllin glycosides (Figure 1).

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Address correspondence to Zhao Yu, Institute of Nautical Medicine, Nantong University, 19 Qixiu Road, Nantong, Jiangsu 226001, China. E-mail: zhaoyoo@163.com

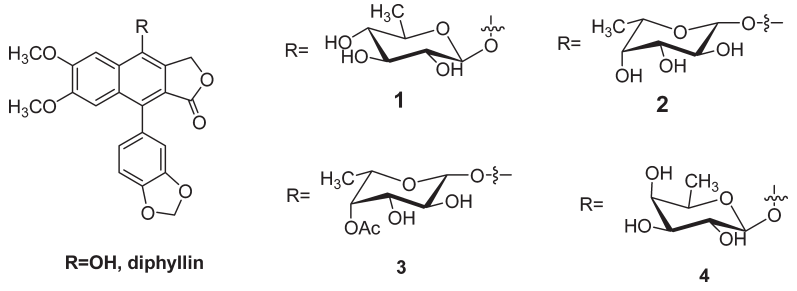


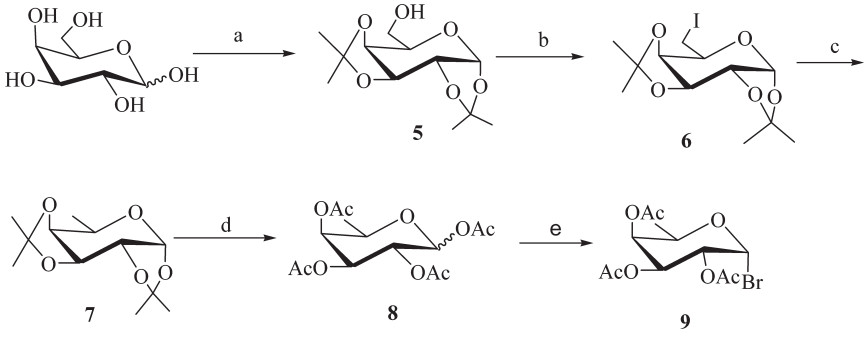
Figure 1: Structures of diphyllin and its glycosides.

RESULTS AND DISCUSSION

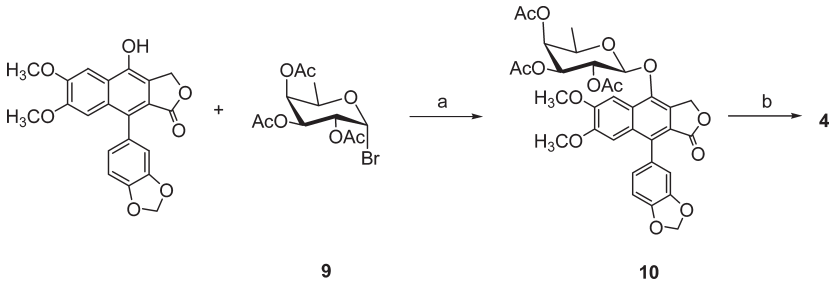
Per-*O*-acetyl-D-fucosyl bromide was used as starting material in this project. The synthesis of D-fucose from D-galactose has been reported.[10] We found that direct iodination of **5** with I_2/triphenylphosphine/imidazole[11] and reduction with tributyl hydride[12] could be successfully applied to prepare D-fucosyl moiety, and this method provided better yield than the former procedure (Scheme 1).

Diphyllin was easily prepared for 2-bromo-4,5-dimethoxybenzaldhyde in five steps in 42.5% yield according to the procedure reported by Charlton et al.[13] The glycosylation of diphyllin with donor **9** was performed in $0.1\ mol \cdot L^{-1}$ $NaOH/H_2O$ in the presence of tetra-butylammonium bromide (TBAB, 1.0 equiv) at 40°C to give **10**. Subsequently, deacetylation with K_2CO_3 in methanol was carried out smoothly to produce target molecule without destruction of the lactone residue (Sch. 2).

Compounds were evaluated for their cytotoxic activities against three human cancer cell lines HCT116, MCF-7, and KB using a SRB growth



Scheme 1: Reagents and conditions: a) CH_3COCH_3, $CuSO_4$, H_2SO_4, 74.3%; b) I_2, imidazole, Ph_3P, $PhCH_3$, 90.8%; c) Bu_3SnH, AIBN, $PhCH_3$, 75.7%; d) 80% HOAc, 120°C, then Ac_2O, Pyr, 80.9%; e) HBr-HOAc, DCM, 78.6%.



9 10

Scheme 2: Reagents and conditions: a) $CHCl_3$, H_2O, TBAB, NaOH, 40°C, 80.6%; b) K_2CO_3, MeOH, 83.3%.

inhibition assay. IC_{50} values are summarized in Table 1 and represent the concentration inducing a 50% decrease of cell growth after 3 days incubation.

The synthesized analog **4** showed potent biological activities against three human cancer cell lines. Especially, **4** was more cytotoxic than **1** and **2** to the MCF-7 cell line, suggesting that the stereochemical orientation of C-4" hydroxyl group has a significant impact on cytotoxic effect.

EXPERIMENTAL

General Methods

Solvents were purified in the usual way. TLC was performed on precoated Merck silica Gel 60 F_{254} plates. Flash chromatography was performed on silica gel (100–200 mesh, Qingdao, China). Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter. ^1H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 MHz spectrometer with tetramethylsilane (TMS) as an internal standard, and chemical shifts were recorded in δ values. The high-resolution spectra were obtained on a Q-TOF Global Mass (ESIMS).

*1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**5**)*

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (2) was prepared by acetonation of D-galactose,[9] R_f 0.67 (EtOAc:petroleum ether, 1:2), $[\alpha]_D^{20}$ −55.3° (c 3.5, $CHCl_3$), ^1H NMR ($CDCl_3$): δ 5.58 (d, 1 H, $J = 5.0$ Hz, H-1), 4.61 (dd, 1 H,

Table 1: IC_{50} values (μM) for 1, 2, 4 and diphyllin.

No.	HCT116	MCF-7	KB
1	0.05	>100	0.03
2	0.9	50	0.9
4	2.8	2.4	0.2
Diphyllin	0.5	60	0.06

$J = 7.8$, 2.3 Hz, H-3), 4.34 (dd, 1 H, $J = 5.0$, 2.3 Hz, H-2), 4.28 (d, 1 H, $J = 8.3$ Hz, H-4), 3.88–3.85 (m, 2 H, H-6a, 6b), 3.75–3.73 (m, 1 H, H-5), 2.19 (brs, 1 H, OH-6), 1.53, 1.46, 1.34, 1.33 (s, each 3 H, CH_3), identical to literature.[9]

*1,2:3,4-Di-O-isopropylidene-6-iodo-D-galactopyranose (**6**)*[10]

I_2 (2.1 g, 8.3 mmol), Ph_3P (2.3 g, 8.7 mmol), and imidazole (1.2 g, 17.6 mmol) were added to the solution of **5** (1.5 g, 5.8 mmol) in toluene (30 mL). The mixture was stirred for 2 h in an oil bath at 70°C. The mixture was diluted and filtered, and the filter concentrated in vacuo and purified by silica gel chromatography (EtOAc:petroleum ether, 1:4) to afford **6** as white solid (1.9 g, 90.8%), $\mathbf{R}_f$ 0.76 (EtOAc:petroleum ether, 1:2), $[\alpha]_D^{20}$ −57.3° (c 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 5.54 (d, 1 H, $J = 5.0$ Hz, H-1), 4.62 (dd, 1 H, $J = 7.8$, 2.3 Hz, H-3), 4.41 (dd, 1 H, $J = 7.8$, 1.9 Hz, H-4), 4.30 (dd, 1 H, $J = 5.0$, 2.3 Hz, H-2), 3.96–3.93 (m, 1 H, H-5), 3.32 (dd, 1 H, $J = 9.8$, 6.9 Hz, H-6a), 3.21 (dd, 1 H, $J = 9.8$, 7.3 Hz, H-6b), 1.54, 1.44, 1.35, 1.33 (s, each 3 H, CH_3).

*1,2:3,4-Di-O-isopropylidene-D-fucopyranose (**7**)*[10]

Bu_3SnCl (3 g, 9.0 mmol) was dissolved in ether (20 mL); $LiAlH_4$ (150 mg, 3.5 mmol) was added carefully at 0°C. The mixture was allowed to stir for 2 h at rt. Ice water (10 mL) was added, and the mixture was stirred for an additional 10 min. The organic layer was successively washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the Bu_3SnH as oil.

The resulted Bu_3SnH was dissolved in $PhCH_3$ (20 mL) and **6** (1.8 g, 4.8 mmol) and AIBN (117 mg, 0.7 mmol) was added. The mixture was stirred for 1 h at 100°C under N_2, and then EtOAc (20 mL) was added. The organic layer was washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:30) to afford **7** as oil (890 mg, 75.7%), $\mathbf{R}_f = 0.65$ (EtOAc:petroleum ether, 1:10), $[\alpha]_D^{20}$ −35.6° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.52 (d, 1 H, $J = 5.0$ Hz, H-1), 4.59 (dd, 1 H, $J = 7.8$, 2.3 Hz, H-3), 4.29 (dd, 1 H, $J = 5.0$, 2.3 Hz, H-2), 4.08 (dd, 1 H, $J = 7.8$, 1.8 Hz, H-4), 3.93–3.89 (m, 1 H, H-5), 1.52, 1.47, 1.35, 1.33 (s, each 3 H, CH_3), 1.26 (d, 3 H, $J = 6.4$ Hz, CH_3).

*1,2,3,4-Tetra-O-acetyl-D-fucopyranose (**8**)*[10]

7 (1.1 g, 4.7 mmol) was dissolved in 80% HOAc (20 mL), and stirred for 12 h at 110°C. The mixture was evaporated under reduced pressure. The residue was dissolved in dry pyridine (10 mL) and Ac_2O (5 mL), and DMAP (20 mg) was added slowly. The mixture was stirred for 2 h. CH_2Cl_2 (30 mL) was added, and the organic layer was washed with 1 M HCl (2 × 30 mL), saturated

$NaHCO_3$ (2 × 30 mL), and brine (2 × 30 mL) and successively dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:3) to give afford **8** (1.25 g, 80.9%, α:β, 4:5), $\mathbf{R}_f = 0.35$ (EtOAc:petroleum ether, 1:3), HRMS calcd for $C_{14}H_{20}O_9Na$ 355.1005, found 355.0999; ^{1}H NMR($CDCl_3$): β: δ 5.68 (d, 1 H, $J = 8.3$ Hz, H-1), 5.34–5.33 (m, 2-H, H-2, H-3), 5.07 (dd, 1 H, $J = 10.1$, 3.2 Hz, H-4), 3.98–3.94 (m, 1 H, H-5), 2.19, 2.11, 2.04, 1.99 (s, each 3 H, OAc), 1.22 (d, 3 H, $J = 6.4$ Hz, CH_3); α: δ 6.34 (d, 1 H, $J = 3.2$ Hz, H-1), 5.30–5.27 (m, 2 H, H-2, H-3), 4.28 (dd, 1 H, $J = 13.3$, 6.4 Hz, H-4), 4.14–4.10 (m, 1 H, H-5), 2.18, 2.15, 2.09, 2.00 (s, each 3 H, OAc), 1.16 (d, 1 H, $J = 6.4$ Hz, CH_3).

*2,3,4-Tri-O-acetyl-D-fucopyranosyl bromide (**9**)*

8 (1.3 g, 4.0 mmol) was dissolved in dry DCM (10 mL); 40% HBr-HOAc (2 mL) was added carefully at 0°C. The mixture was allowed to stir for 4 h at rt. DCM (10 mL) was added, and the organic layer was successively washed with saturated $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give **9** (1.10 g, 78.6%) as a white solid.

*2, 3, 4-Tri-O-acetyl-7-O-β-D-fucopyranosyldiphyllin (**10**)*

To the solution of diphyllin (200 mg, 0.53 mmol) and TBAB (171 mg, 0.53 mmol) in $CHCl_3$ (20 mL) was added aqueous 0.1 mol/L NaOH (20 mL). After stirring for 10 min at 40°C, **9** (302 mg, 0.79 mmol) was added, and the two-phase mixture was stirred for 6 h at 40°C. Then $CHCl_3$ (20 mL) was added and the resulting organic phase was washed with brine (2 × 20 mL) and dried over Na_2SO_4, and the solvent evaporated under reduce pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:2) to afford **10** as white solid (278 mg, 80.6%), $\mathbf{R}_f$ 0.55 (EtOAc:petroleum ether, 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, 1 H, $J = 1.8$ Hz, ArH), 7.06 (s, 1 H, ArH), 6.95 (d, 1 H, $J = 7.8$ Hz, ArH), 6.82 (dd, 1 H, $J = 5.5$, 1.4 Hz, ArH), 6.80–6.78 (m, 1 H, ArH), 6.09 (s, 1 H, OCH_2O), 6.05 (d, 1 H, $J = 1.4$ Hz, OCH_2O), 5.68 (dd, 1 H, $J = 10.6$, 8.2 Hz, H-1"), 5.34 (d, 1 H, $J = 3.2$ Hz, H-4"), 5.15–5.13 (m, 2 H, H-2", H-3"), 5.50 (dd, 1 H, $J = 14.7$, 1.9 Hz, H-9a), 5.41 (dd, 1 H, $J = 14.7$, 3.7 Hz, H-9b), 4.08 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.27, 2.09, 2.05 (each 3 H, 3 × OAc), 1.29 (dd, 1 H, $J = 6.4$, 1.4 Hz, CH_3).

*7-O-β-D-fucopyranosyldiphyllin (**4**)*

The solid **10** (223 mg, 0.32 mmol) was dissolved in CH_3OH (20 mL), and then K_2CO_3 (100 mg, 0.72 mmol) was added. After stirring for 30 min at rt, the solution was neutralized with 1 mol/L HCl, $CHCl_3$ (20 mL) was added, the resulting organic phase was washed with brine (2 × 20 mL) and dried

over Na_2SO_4, and the solvent evaporated under reduce pressure. The residue was purified by flash chromatography ($CHCl_3$:MeOH, 10:1) to afford **4** as a white solid (150 mg, 83.3%), $\mathbf{R_f}$ 0.40 ($CHCl_3$:MeOH, 10:1), $[\alpha]_D^{25} = -57.3^\circ$ (c1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, DMSO-d_6) : δ 8.18 (d, 1 H, $J = 2.8$ Hz, ArH), 7.03 (dd, 1 H, $J = 7.8$, 1.9 Hz, ArH), 6.98 (d, 1 H, $J = 3.2$ Hz, ArH), 6.93 (dd, 1 H, $J = 17.4$, 1.9 Hz, ArH), 6.81–6.78 (m, 1 H, ArH), 6.12 (s, 2 H, OCH_2O), 5.77 (brs, 1 H, OH-2"), 5.52 (dd, 1 H, $J = 14.8$, 3.7 Hz, H-9a), 5.47 (d, 1 H, $J = 14.8$ Hz, H-9b), 4.96 (brs, 1 H, OH-3"), 4.71 (d, 1 H, $J = 7.7$ Hz, H-1"), 4.68 (brs, 1 H, OH-4"), 3.94 (s, 3 H, OCH_3), 3.76–3.72 (m, 1 H, H-2"), 3.66 (s, 3 H, OCH_3), 3.63–3.60 (m, 1 H, H-5"), 3.47–3.46 (m, 1 H, H-4"), 3.43–3.42 (m, 1 H, H-3"), 1.18 (dd, 3 H, $J = 6.4$, 1.2 Hz, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6): δ 169.1 (C=O), 151.3 (C-5), 149.9 (C-4), 146.9 (C-4'), 146.8 (C-3'), 145.0 (C-7), 134.8 (C-7'), 129.9 (C-1), 129.7 (C-8), 128.2 (C-1'), 126.9 (C-2), 123.5 (C-6'), 118.6 (C-8'), 110.8 (C-2'), 107.9 (C-3), 105.7 (C-1"), 105.3 (C-5), 101.8 (C-6), 101.1 (OCH_2O), 73.2 (C-3"), 70.8 (C-4"), 70.5 (C-2"), 70.4 (C-5"), 67.1 (C-9), 55.7 (OCH_3), 55.1 (OCH_3), 16.5 (CH_3); HRMS calcd for $C_{27}H_{27}O_{11}$ 527.1553, found 527.1576.

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