Fluorous Oligosaccharide Synthesis Using a Novel Fluorous Protective Group

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Supporting Information

Compound 3: β -Alanine ethyl ester hydrochloride (**1**; 5.65 g, 36.9 mmol) and K_2CO_3 (17.0 g, 123 mmol) were added to a solution of compound **2** (7.59 g, 12.3 mmol) in dry CH_3CN (200 mL) at room temperature. After 17 h reflux, the reaction mixture was extracted with AcOEt. The AcOEt layers were washed with 2M HCl, saturated $NaHCO_3$, and brine. The organic layers were dried over anhydrous Na_2SO_4 , and evaporated. Almost pure **3** (5.89 g, 83 %) obtained thus was used in next step without further purification. Compound **3**, pale yellow oil, 1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.3 Hz, 3H), 1.77 (m, 2H), 2.16 (m, 2H), 2.50 (t, J = 6.3 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H), 4.15 (q, J = 7.3 Hz, 2H).

Compound 5 a : Triethylamine (4.27 mL, 30.6 mmol) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP; 6.37 g, 12.2 mmol) were added to a solution of compound **3** (5.89 g, 10.2 mmol) and **4** (5.27 g, 10.7 mmol) in dry CH_2Cl_2 (160 mL) at room temperature. After stirring for 3h at room temperature, 5% citric acid was added to the reaction mixture. The reaction mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated. The crude product was purified by column chromatography on silica gel (hexane-AcOEt, 4:1) to give compound **5a** (9.98 g, 93%) as colorless oil. Compound **5a**, white powder, 1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (m, 3H), 1.87 (m, 2H), 2.10 (m, 2H), 2.61 (m, 6H), 3.45 (m, 2H), 3.64 (m, 2H), 4.16 (m, 2H); MALDI-TOF-MS: Calcd for $C_{27}H_{20}F_{34}NO_3$ ($M+H^+$): 1052.1, Found: 1051.1.

Compound 6: A 1M sodium hydroxide aqueous solution (80 mL) was added to a solution of compound **5a** (9.98 g, 9.49 mmol) in 1,4-dioxane (160 mL) at room temperature. After stirring for 4 h at 70 $^{\circ}C$, 2M HCl was added, and the reaction mixture was adjusted to pH 2. The reaction

mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated. The almost pure **6** (9.52 g, 98 %) was used in next step without further purification. Compound **6**, white powder, ¹H NMR (400 MHz, CDCl₃-CD₃OD = 5: 3): δ = 1.92 (m, 2H), 2.15 (m, 2H), 2.65 (m, 6H), 3.49 (m, 2H), 3.66 (m, 2H); MALDI-TOF-MS: Calcd for C₂₅H₁₆F₃₄NO₃ (M+H⁺): 1024.1, Found: 1022.6; Calcd for C₂₅H₁₅F₃₄NO₃Na (M+Na⁺): 1046.1, Found: 1044.6.

Introduction of Bfp group to carbohydrate: 4-(Dimethylamino)pyridine (139 mg, 1.14 mmol) and dicyclohexylcarbodiimide (353 mg, 1.71 mmol) were added to a solution of compound **7** (124 mg, 0.285 mmol) and **6** (1.05 g, 1.03 mmol) in dry CH₂Cl₂ (25 mL). After stirring for 2 h at room temperature, toluene (20 mL) was added to the reaction mixture. The reaction mixture was extracted three times with FC-72 (20 mL×3). The combined FC-72 layers were evaporated. The almost pure **8** (865 mg, 87 %) was used in next step without further purification.

Removal of Bfp group from carbohydrate: A 5M sodium methoxide solution in methanol (10 μL) was added to a solution of compound **11** (43 mg, 12.1 μmol) in Et₂O (2 mL) and MeOH (2 mL) at room temperature. After stirring for 1 h at room temperature, Amberlite IR-120 (H⁺ form) was added, and the reaction mixture was neutralized. After filtration, the filtrate was evaporated. The residue was partitioned between MeOH and FC72. The methanol layer was evaporated to give compound **12** (4.0 mg, 93 %). The FC72 layer was evaporated to give compound **5b** (35.0 mg, 93 %).

Glycosylation procedure (Compound 14): Molecular Sieves AW-300 (700 mg) was added to a solution of compound **9** (142 mg, 442 μmol) and **13** (152 mg, 221 μmol) in dry ether (5 mL) under argon atmosphere. After stirring for 1 h at room temperature, TMS-OTf (8 μL, 442 μmol) was added to the reaction mixture at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture was filtered. The filtrate was added to saturated NaHCO₃, and extracted three times with AcOEt. The AcOEt layers were washed with brine, dried over anhydrous Na₂SO₄, and evaporated. The residue was partitioned between MeOH and FC72. The FC72 layer was evaporated to give compound **14** (124 mg, 75 %). The almost pure **14** was used in next step without further purification.

Compound 15: To a solution of compound **14** (95 mg, 25.4 mmol) in dry THF (2 mL) was added 70% HF-pyridine (180 μL) at room temperature. After stirring for 8 h at room temperature, the

reaction mixture was partitioned between toluene, saturated NaHCO_3 , and FC72. The FC72 layer was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated to give compound **15** (85 mg, 95 %). The almost pure **15** was used in next step without further purification.

Compound **16**, **17**, **18**, and **19** were prepared by repeating the same procedures.