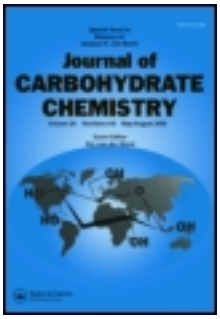

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Synthesis of Floridoside

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Synthesis of Floridoside

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Floridoside (2-*O*-glycerol-α-D-galactopyranoside) is a natural glycerol glycoside found in red algae and is believed to play important roles in carbon storage, transport, and assimilation and in the regulation of osmotic balance. We describe here a rapid, high-yield, and high-stereoselectivity synthesis of floridoside in which the key step involves the 1,2-*cis O*-glycosylation of 1,3-dibenzylglycerol with ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside using iodonium dicollidine perchlorate (IDCP) or N-iodosuccinimide/trimethylsilyl triflate (NIS/TMSOTf) as promoters.

Keywords Floridoside; Glycerol glycoside; 1,2-*cis O*-glycosylation; Thioglycoside

INTRODUCTION

Floridoside (2-*O*-glycerol-α-D-galactopyranoside) (Figure 1), first isolated from Rhodophyceae *Rhodymenia palmata* in 1930 by Colin and Guéguen,[1] is a natural glycerol galactoside found in red algae. Floridoside is believed to play a crucial role as the main photosynthetic reserve product[2–4] and in the control of intracellular osmotic regulation.[5–7] Moreover, it is the carbon precursor for the synthesis of cell-wall polysaccharides in the red microalga *Porphyridium* sp. (Rhodophyta).[8] The overall metabolism of floridoside in red algae involves its synthesis by floridoside phosphate synthase,[9] its degradation by α-galactosidase, and the interconversion of UDP-galactose and UDP-glucose catalyzed by UDP-D-galactose-4-epimerase.[10] Floridoside is a potent inhibitor of cyprid settlement at nontoxic concentrations to nauplii (0.01 mg/mL^{-1})[11] and possess feeding-deterrent activity against the sea urchin *Strongylocentrotus intermedius*.[12] Its crystal structure, chirality,[13] and complete ^{1}H and ^{13}C spectral assignment[14] have been recently described after extraction and purification from algae. However, this process of isolation is complex and usually furnishes a low amount of floridoside. Thus, studies of the physiological

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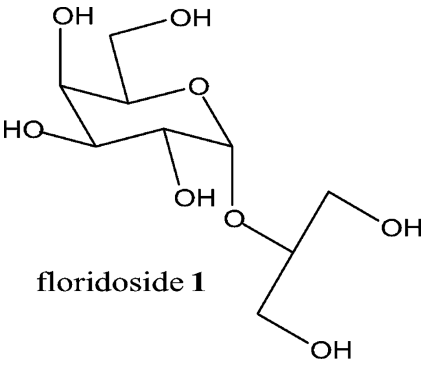


floridoside **1**

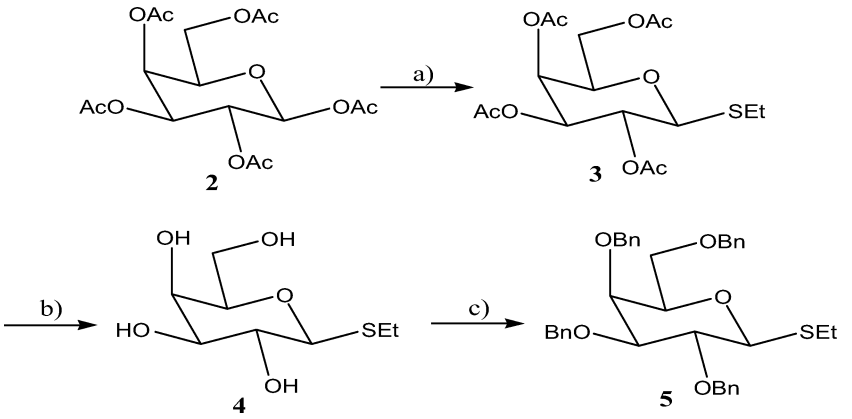
Figure 1: Structure of floridoside.

roles of floridoside remain difficult. While the synthesis of some glycosyl glycerols has been described with good yields,[15,16] the synthesis of floridoside, reported in 1965 by Austin et al., afforded only a 27% isolated yield using a chloride donor and silver perchlorate and silver carbonate promoter.[17] We describe here a rapid, high-yield, and high-stereoselectivity synthesis of floridoside involving the 1,2-*cis* *O*-glycosylation of 1,3-dibenzylglycerol with ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside using iodonium dicollidine perchlorate (IDCP) or N-iodosuccinimide/trimethylsilyl triflate (NIS/TMSOTf) as promoters.

RESULTS AND DISCUSSION

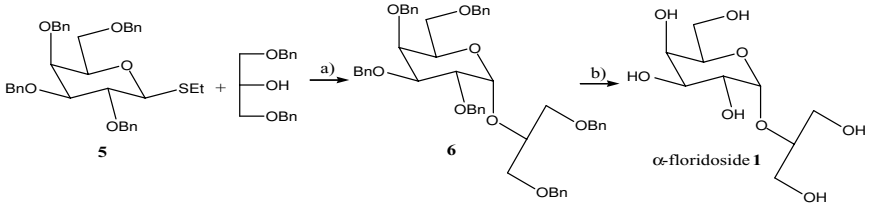
The synthesis of floridoside (2-*O*-glycerol-α-D-galactopyranoside) **1** requires a stereoselective 1,2-cis *O*-glycosylation. Although the stereoselectivity of the glycosylation reaction is influenced by a number of other parameters, such as temperature, solvent, concentration, and the nature of the promoter, the presence of a nonparticipating group at the C-2 position (most commonly a benzyl group) is the principle method used for the stereoselective synthesis of 1,2-cis *O*-glycosides.[18] The nature of the leaving group in the glycosyl donor is also of great importance, and thioglycosides have been successfully applied to 1,2-cis *O*-glycosylation reactions.[19] Thioglycoside **5** (Sch. 1) was thus selected as a potential donor for this glycosylation reaction. Commercially available per-*O*-acetylgalactopyranose **2** was treated with ethyl mercaptan in the presence of catalytic amounts of indium (III) chloride and titanium (IV) chloride to afford the corresponding thioglycoside in 85% yield.[20] Removal of the acetyl groups using sodium methoxide in methanol afforded **4**, which was benzylated using sodium hydride and benzyl bromide. The desired thioglycoside donor **5** was obtained in 88% yield (75% overall yield over three steps).

Thioglycoside donor **5** was then engaged in glycosylation reactions using commercially available acceptor 1,3-dibenzyloxy-2-propanol (Sch. 2). Different



Scheme 1: Synthesis of the thioglycoside donor 5. a) EtSH, $InCl_3/TiCl_4$, CH_3CN, 85%; b) MeONa/MeOH, quant. c) NaH, BnBr, DMF, 88%.

promoters were tested to optimize the yield and stereoselectivity of the glycosylation reaction. As previously demonstrated by Demchenko et al.,[21] IDCP and NIS/TMSOTf are effective promoters in 1,2-cis *O*-glycosylation reactions involving thioglycosides. Both of these promoters were tested for the glycosylation of 1,3-dibenzyloxy-2-propanol with thioglycoside donor **5**.



Scheme 2: Synthesis of α-floridoside. a) IDCP, MS 4 Å, toluene/dioxane 1/3, rt, 1 hr, 67% (α/β 5/1) or NIS/TMSOTf, MS 4 Å, toluene/dioxane 1/3, 0°C, 1.5 hr, 88% (α/β 8/1). b) H_2 (1 atm) Pd-C, MeOH, rt, 24 hr, quant.

IDCP is not commercially available and was synthesized in two steps following literature procedures.[22] When IDCP was used as promoter, the maximum yield of perbenzylated galactosyl glycerol **6** was 67% with a moderate α/β selectivity of 5/1. This modest yield could be explained by the presence of a side product, 2,3,4,6-tetrabenzyl-β-D-galactopyranose, resulting from the presence of traces of water in IDCP. The use of a combination of NIS and TMSOTf afforded an improved yield and higher stereoselectivity, and no 2,3,4,6-tetrabenzyl-β-D-galactopyranose was observed on TLC after completion of the reaction. When the reaction was performed at 0°C, perbenzylated galactosyl glycerol **6** was formed in 88% yield and α/β ratio of 8/1. Column chromatography on silica gel, using petroleum ether/ethyl acetate 9/1 as the eluent, afforded the pure α-anomer as a viscous and colorless oil (71% isolated yield).

Debenzylation using 10% Pd/C under hydrogen atmosphere afforded floridoside **1** as a white solid in quantitative yield. Floridoside **1** was thus obtained in five steps from commercially available per-*O*-acetylgalactopyranose with an overall yield of 53%.

CONCLUSION

We have described a rapid and high-yield synthesis of floridoside involving a highly stereoselective 1,2-*cis* *O*-glycosylation reaction between ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside and 1,3-dibenzylglycerol in the presence of iodonium dicollidine perchlorate (IDCP) or N-iodosuccinimide/trimethylsilyl triflate (NIS/TMSOTf). This new pathway will allow easy access to large quantities of floridoside and facilitate studies of its physiological roles.

EXPERIMENTAL

General

All chemicals were purchased from Aldrich or Acros and used without further purification. Solvents were dried and distilled using classical procedures and stored on molecular sieves 4 Å. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded at rt, in $CDCl_3$ or D_2O (Varian, 500 MHz). Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. HRMS and LRMS were recorded on Micromass Autospec high-resolution mass spectrometer and Agilent 1100 series LC/MSD trap, respectively. Thin-layer chromatography (TLC) was carried out using Merck plates of silica gel 60 with fluorescent indicator and revealed with UV light (254 nm) when possible and 5% H_2SO_4 in EtOH. Optical rotations were measured at rt using a Perkin Elmer 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories Inc. using a Perkin Elmer 240 CHN Analyzer. Flash chromatography was performed using silica gel 230–400 mesh (Natland International Corporation).

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (3)

To a stirred solution of per-*O*-acetyl-D-galactopyranose (4.683 g, 12 mmol) in freshly distilled acetonitrile (50 mL), ethyl mercaptan (2.67 mL, 36 mmol) and $InCl_3$ (536 mg, 2.4 mmol) were added at rt, followed by the addition of $TiCl_4$ (264 μL, 2.4 mmol), and the reaction was monitored by TLC. At the end point the reaction mixture was diluted with ethyl acetate and washed successively with saturated aq. Na_2CO_3 and brine, dried (Na_2SO_4), and concentrated. Filtration of the crude product through a short column of silica gel afforded **3** in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.43 (1H, d, $J = 3.3$ Hz, H-4),

5.23 (1H, t, $J = 9.7$ Hz, H-2), 5.04 (1H, dd, $J = 10.0$ Hz and $J = 3.3$ Hz, H-3), 4.49 (1H, d, $J = 9.7$ Hz, H-1), 4.18–4.09 (2H, m, 2H-6), 3.94 (1H, td, $J_t = 7.0$ Hz, $J_d = 1.0$ Hz, H-5), 2.78–2.65 (2H, m, CH_2 SEt), 2.15, 2.06, 2.03, 1.98 (12H, 4 s, 4 Ac), 1.28 (3H, t, $J = 7.5$ Hz, CH_3 SEt). ESIMS *m/z*, calcd for $C_{16}H_{24}O_9SNa$ $[M+Na]^+$ 415.1, found 415.1.

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-galactopyranoside (5)

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-galactopyranoside **3** (5.2 g, 13.3 mmol) was dissolved in anhydrous methanol (40 mL) and NaOMe/methanol solution 1 M (70 mL, 70 mmol) was added slowly at rt. The course of the reaction was monitored by TLC. After 1 hr, the reaction was complete and was neutralized by addition of Amberlite IR 120 (H^+ form). After filtration, the solvent was evaporated and a white solid of ethyl-1-thio-*β*-D-galactopyranoside **4** (3.0 g, quantitative) was obtained and used without further purification. Ethyl-1-thio-*β*-D-galactopyranoside **4** (2.67 g, 11.9 mmol) was then dissolved in anhydrous dimethylformamide (DMF, 20 mL) and slowly added to a suspension of sodium hydride (NaH, 60 mmol) in anhydrous DMF (35 mL) at 0°C. After 10 min, a solution of benzyl bromide (5.8 mL, 48.8 mmol) in anhydrous DMF (20 mL) was added slowly and the mixture was allowed to reach rt. After completion of the reaction, ethyl acetate (200 mL) was added and the organic phase was washed with water and 0.1 M HCl. Purification of the residue on silica gel using petroleum ether/ethyl acetate 9/1 to 8/2 as the eluent afforded **5** as a white solid, in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.20–7.10 (20H, m, H Ar), 4.96 (1H, d, $J =$ 11.7 Hz, 1H CH_2 Bn), 4.89 (1H, d, $J = 10.1$ Hz, 1H CH_2 Bn), 4.81 (1H, d, $J = 10.1$ Hz, 1H CH_2 Bn), 4.74 (2H, s, CH_2 Bn), 4.63 (1H, d, $J = 11.7$ Hz, 1H CH_2 Bn), 4.50–4.40 (2H, m, CH_2 Bn), 4.43 (1H, d, $J = 9.5$ Hz, H-1), 3.97 (1H, d, $J = 2.2$ Hz, H-4), 3.84 (1H, t, $J = 9.5$ Hz, H-2), 3.60–3.50 (4H, m, H-3, H-5, 2 H-6), 2.79-2.63 (2H, m, CH_2 SEt), 1.31 (t, $J = 7.4$ Hz, CH_3 SEt). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 138.64, 138.27, 138.19, 137.76 (four quaternary aromatic carbons), 128.35, 128.33, 128.27, 128.22, 128.18, 128.15, 128.13, 128.08, 127.94, 127.84, 127.81, 127.79, 127.77, 127.71, 127.64, 127.56, 127.54, 127.48, 127.46, 127.44 (20 CH Ar), 85.21 (C-1), 83.98 (C-3), 78.33 (C-2), 77.09 (C-4), 75.68 (C-5), 74.33, 73.45, 72.56 (4 CH_2 OBn), 68.70 (C-6), 24.69 (CH_2 SEt), 15.01 (CH_3 SEt). ESIMS *m/z*, calcd for $C_{36}H_{40}O_5SNa$ $[M+Na]^+$ 607.2, found 607.2 and for $C_{36}H_{40}O_5SK$ $[M+K]^+$ 623.2, found 623.2.

2-(Phenylmethoxy)-1-[(phenylmethoxy)methyl]ethyl-2,3,4,6-tetrakis-O-(phenylmethyl)-α-D -galactopyranoside (6)

A mixture of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-*β*-D-galactopyranoside **5** (100 mg, 0.171 mmol) and 1,3-dibenzyloxy-2-propanol (46 mg, 0.163 mmol) was

dissolved in toluene (5 mL) and evaporated under reduced pressure. This operation was repeated twice. Freshly activated (300°C for 2 h in vacuo) molecular sieves 4 Å (244 mg), freshly distilled toluene (2 mL), and dioxane (6 mL) were added and the mixture was stirred for 1 hr at rt. The mixture was cooled to 0°C and IDCP (115 mg, 0.245 mmol) or NIS (46 mg, 0.204 mmol) and TMSOTf (19 μL, 0.098 mmol) were added and the course of reaction was monitored by TLC. When the reaction was finished (1.5 hr), the molecular sieves were filtered off and washed with dichloromethane (70 mL). The filtrate was then washed with aqueous $Na_2S_2O_3$ (2 × 20 mL) and water (3 × 20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification on silica gel, using petroleum ether/ethyl acetate 9/1 as the eluent, afforded the pure α-anomer as a viscous and colorless liquid, in 71% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.41–7.22 (30H, m, HAr), 5.27 (1H, t, $J = 3.3$ Hz, H-1), 4.96 (1H, dd, $J = 11.4$ Hz, $J = 2.9$ Hz, 1H CH_2 Bn), 4.87 (1H, dd, $J = 11.7$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.75 (1H, dd, $J = 11.7$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.72 (2H, d, $J = 2.8$ Hz, CH_2 Bn), 4.59 (1H, dd, $J = 11.4$ Hz and $J = 2.9$ Hz, 1H CH_2 Bn), 4.54 (2H, d, $J = 2.4$ Hz, CH_2 Bn), 4.52 (1H, dd, $J = 11.8$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.48 (1H, dd, $J = 11.8$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.40 (1H, dd, $J = 11.8$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.36 (1H, dd, $J = 11.8$ Hz and $J = 2.6$ Hz, 1H CH_2 Bn), 4.23–4.19 (1H, m, H-4), 4.17–4.11 (1H, m, H-1′), 4.06 (1H, dt, $J_d = 9.6$ Hz and $J_t = 3.4$ Hz, H-2), 3.98 (1H, dt, $J_d = 9.6$ Hz and $J_t = 2.9$ Hz, H-3), 4.00 (1H, d, $J = 2.9$ Hz, H-5), 3.68–3.48 (6H, m, 4H-2', 2H-6). ^{13}C NMR (125 MHz, $CDCl_3$)δ (ppm): 139.26, 139.05, 138.93, 138.58, 138.48, 138.40 (six quaternary aromatic carbons), 128.61, 128.59, 128.58, 128.47, 128.43, 128.08, 128.02, 127.87, 127.84, 127.81, 127.79, 127.77, 127.74, 127.69, 127.66 (30 CH Ar), 97.24 (C-1), 79.18 (C-3), 76.55 (C-2), 75.40 (C-4), 75.03 (CH_2 Bn), 75.00 (CH_2 Bn), 73.62 (C-1′), 73.60 (CH_2 Bn), 73.38 (CH_2 Bn), 73.36 (CH_2 Bn), 72.91 (C-5), 70.81 (CH_2 Bn), 70.65 (1C-2'), 69.45 (1C-2'), 69.17 (C-6). ESIMS m/z, calcd for $C_{51}H_{54}O_8Na$ $[M+Na]^+$ 817.4, found 817.4. HRMS calcd for $C_{51}H_{54}O_8Na$ 817.3716, found 817.3703. Elem. anal. calcd for $C_{51}H_{54}O_8$: C, 77.05; H, 6.85. Found: C, 76.72; H, 7.00.

Floridoside (2-*O*-α-D-galactopyranosylglycerol) (1)

2-Benzyl-1-(benzylmethyl)ethyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside **6** (58 mg, 0.073 mmol) in methanol (2 mL) was stirred under hydrogen atmosphere in the presence of palladium on activated carbon (10%, 7 mg) for 2 d at rt. The resulting mixture was filtered through celite and washed with methanol. After evaporation of the solvent, floridoside (18 mg) was recovered as a white solid in quantitative yield. $[\alpha]_D$+168° (c 0.02, water), lit. $[\alpha]_D$+164° (c 0.97, water), ^{1}H NMR (500 MHz, D_2O) δ (ppm): 5.14 (1H, d, $J = 3.9$ Hz, H-1), 4.09 (1H, t, $J = 6.2$ Hz, H-5), 3.99 (1H, d, $J = 3.3$ Hz, H-4), 3.89 (1H,

dd, $J = 10.0$ Hz and $J = 3.3$ Hz, H-3), 3.82 (1H, dd, $J = 10.0$ Hz and $J = 3.9$ Hz, H-2), 3.73 (2H, d, $J = 6.2$ Hz, 2H-6), 3.82–3.68 (5H, m, H-1′, 4H-2′). ^{13}C NMR (125 MHz, D_2O) δ (ppm): 100.98 (C-1), 81.60 (1 C-2′), 73.92 (C-5), 72.18 (C-3), 72.12 (C-4), 71.30 (C-2), 64.24 (C-1′), 63.97 (C-6), 63.18 (1 C-2′). ESIMS m/z, calcd for $C_9H_{18}O_8Na$ $[M+Na]^+$ 277.1, found 277.1. HRMS calculated for $C_9H_{18}O_8Na$ 277.0899, found 277.0915.

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