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A new and efficient strategy for the synthesis of shimofuridin analogs: 2′-*O*-(4-*O*-stearoyl-α-L-fucopyranosyl)thymidine and -uridine

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Abstract

Two shimofuridin analogs: 2′-*O*-(4-*O*-stearoyl-α-L-fucopyranosyl)thymidine (**2**) and -uridine (**3**) have been synthesized using D-arabinose, L-fucose, thymine, uracil, and stearoyl chloride as the starting materials. The synthetic procedures involve the facile preparation of 1-(3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**9**) and -uracil (**10**) by coupling of 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**8**) with silylated thymine and uracil, and then stereoselective formation of the 1,2-*cis* (α) interglycoside bonds through condensation of the nucleoside derivatives **9** and **10** with 2-(2,3-di-*O*-benzyl-4-*O*-stearoyl-β-L-fucopyranosylsulfonyl) pyrimidine (**18**). The 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**8**) was prepared by an improved procedure from D-arabinose.

Keywords: Oligosaccharides; Nucleoside; Synthesis

1. Introduction

2′-*O*-[(4″-*O*-(9‴-*O*-Octadienoyl)decatrienoyl)-α-L-fucopyranosyl]inosine (**1**), so-called shimofuridin A (Fig. 1), was isolated from the extract of the Okinawa marine tunicate *Aplidium multiplicatum* Sluiter and identified by Kobayashi and co-workers in 1993.[1] This complex nucleoside derivative was found to have cytotoxic, antimicrobial, and protein kinase C inhibitory activities.

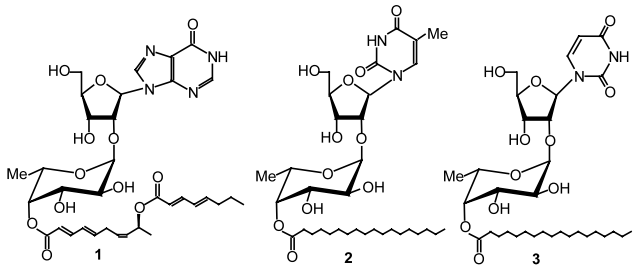

Fig. 1. Shiofuridin A and its analogs.

Subsequently, six new isomers of **1** (i.e., shimofuridins B–G) were isolated from the same tunicate.[2] Shimofuridins B–E differ from shimofuridin A (**1**) in the geometry of the double bonds in the unsaturated acyl chain moieties, while F–G only differ from A in the length (i.e., two additional carbon atoms) of the homologous acyl chains.

So far, a total synthesis of the shimofuridins has not appeared. Only two shimofuridin nucleoside analogs were synthesized by van Boom's and Spencer Knapp's groups by using the naturally available inosine as the starting material.[3,4] With the objective to get an insight into the structure–activity relationships among the shimofuridins, it would be necessary to synthesize shimofuridin analogs containing different nucleosides and side chains. In a preliminary communication, we disclosed a new and versatile approach to the preparation of shimofuridin analogs by using D-arabinose, L-fucose, activated base, and stearoyl chloride as starting materials.[5] In this paper, the synthesis of two shimofuridin analogs: 2′-*O*-(4-*O*-stearoyl-α-L-fucopyranosyl)thymidine (**2**) and -uridine (**3**) (Fig. 1), is presented in detail.

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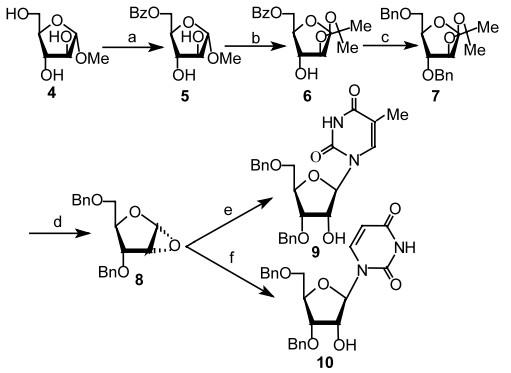
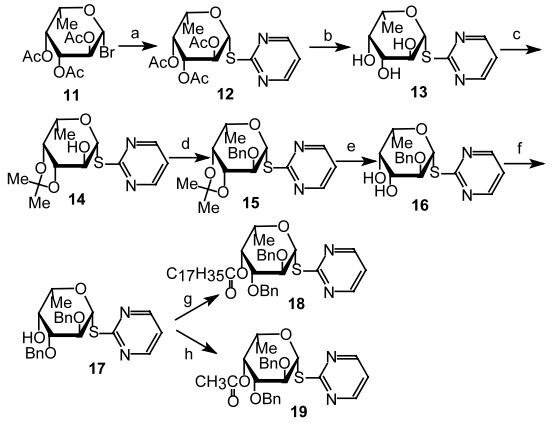


Scheme 1. Reagents and conditions: (a) BzCl (1.0 equiv), pyridine, −5 °C, 3 h, 60%; (b) dry acetone containing 1% HCl, rt, 24 h, 75%; (c) BnCl, toluene, KOH, reflux, 5 h, 85%; (d) (i) 30% AcOH, reflux, 3 h; (ii) TsCl (1.5 equiv), K_2CO_3 (1.5 equiv), pyridine, rt, 12 h; (iii) *t*-BuOK (1.1 equiv), THF, rt, 20 min, 55% overall yield; (e) (i) *O*,*O*-bis-(trimethylsilyl)thymine (1.5 equiv), CH_2Cl_2, 4 Å MS, rt, 8 h; (ii) HCO_2H, rt, 10 min, 87% overall yield; (f) (i) *O*,*O*-bis-(trimethylsilyl)uracil (1.5 equiv), CH_2Cl_2, 4 Å MS, rt, 8 h; (ii) HCO_2H, rt, 10 min, 85% overall yield.



Scheme 2. Reagents and conditions: (a) 2-mercaptopyrimidine (3.0 equiv), tetrabutylammonium hydrogensulfate (1.0 equiv), 1 M aq Na_2CO_3, CH_2Cl_2, rt, 24 h, 96%; (b) CH_3OH, $NaOCH_3$ (cat), rt, 3 h, 100%; (c) $Me_2C(OMe)_2$, acetone, TsOH (cat), rt, 20 h, 81%; (d) BnBr, NaH, DMF, reflux, 5 h, 87%; (e) CH_3OH, H_2SO_4 (cat), rt, 20 h, 90%; (f) (i) CH_3OH, dibutyltin oxide, reflux; (ii) toluene, tetrabutylammonium iodide, BnBr, 50 °C, 18 h, 71%; (g) $C_{17}H_{35}COCl$, pyridine, rt, 3 h, 90%; (h) Ac_2O, pyridine, rt, 2 h, 97%.

2. Results and discussion

In the syntheses of shimofuridin analogs described in the literature,[3,4] the naturally occurring inosine was used as the starting material, and complex procedures for the selective protection of 3′-OH and 5′-OH of the inosine, while leaving 2′-OH free for further coupling reactions, had to be involved. Earlier, we developed a special method for the preparation of nucleoside derivatives with 3′-OH and 5′-OH protected, while maintaining the 2′-OH free. This was achieved by coupling 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**8**) with activated bases in the absence of catalyst.[6] In this report, we use the same strategy to synthesize the free 2′-OH nucleoside derivatives, but the route to compound **8** was slightly improved. Thus, benzoylation of methyl D-arabinofuranoside[7] (**4**) with BzCl in pyridine selectively afforded methyl 5-*O*-benzoyl-D-arabinofuranoside (**5**) (60% yield), which was then converted to the known 5-*O*-benzoyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (**6**)[8] in acetone containing 1% dry HCl in 75% yield (Scheme 1). Benzylation of **6** with BnCl in anhydrous toluene containing KOH under reflux gave the known 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-arabinofuranose[9] (**7**) in 85% yield. The procedure for the preparation of compound **7** from methyl 5-*O*-benzoyl-α-D-arabinofuranoside (**5**) instead of from methyl 5-*O*-tosyl-α-D-arabinofuranoside[9] is simpler and more easily operational. Compound **8** was readily obtained from **7** via removal of the 1,2-*O*-isopropylidene group of **7** in 30% AcOH under reflux, followed by 2-*O*-tosylation with TsCl in pyridine in the presence of K_2CO_3, and subsequent treatment of the tosylate with potassium *tert*-butoxide in dry THF (in 55% overall yield) according to the procedure developed in our lab.[6] Reaction of **8** with trimethylsilylated thymine in the absence of Lewis acid in dry CH_2Cl_2 provided a mixture of the free 2′-OH nucleoside derivative **9** as the major product along with its 2′-*O*-trimethylsilylated nucleoside derivative. The later was converted into **9** by addition of HCO_2H, raising the yield of **9** to 87%. A similar procedure gave the known compound **10**[6] in 85% yield.

With the glycosyl acceptors **9** and **10** in hand, we turned our attention to the synthesis of the fucopyranosyl donor **18**. Treatment of the glycosyl bromide **11**[10] with 2-mercaptopyrimidine and tetrabutylammonium hydrogensulfate in a mixture of CH_2Cl_2 and 1 M aq Na_2CO_3 under phase-transfer conditions[11] at room temperature afforded the fully acetylated 2-(β-L-fucopyranosylsulfanyl)pyrimidine (**12**) in 96% yield (Scheme 2). Deacetylation of **12** with a catalytic amount of sodium methoxide in methanol gave the triol **13**. Treatment of **13** with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetone gave 2-(3,4-*O*-isopropylidine-β-L-fucopyranosylsulfanyl)pyrimidine (**14**) in 81% yield. Benzylation of **14** with BnBr and NaH in dry DMF, followed by hydrolysis in methanol containing a catalytic amount of H_2SO_4, gave **16** in 78% yield for two steps. Selective benzylation of 2-(2-*O*-benzyl-β-L-fucopyranosylsulfanyl)pyrimidine (**16**) with BnBr via its dibutyltin complex gave **17** in 71% yield. The acetylated product **19** further confirms the structure of **17**. Stearoylation of **17** with $C_{17}H_{34}COCl$ in pyridine gave the key intermediate 2-(2,3-di-*O*-benzyl-4-*O*-stearoyl-1-thio-β-L-fucopyranosyl)pyrimidine (**18**) in 90% yield. Condensation of **9** and **10** with **18** in dry CH_2Cl_2 at room temperature in

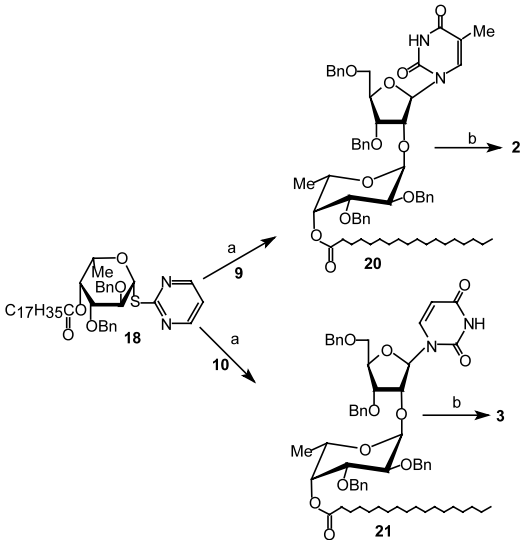
the presence of TMSOTf (0.5 equiv) afforded the blocked target compounds **20** and **21** as the sole products in 88 and 90% yields (based on **9** and **10**), respectively (Scheme 3). The chemical shift δ 5.30 and 5.33 for H-1″ of **20** and **21**, respectively, definitely indicated the α configuration for the fucosyl linkage.[3] The title compounds **2** and **3** were obtained by debenzylation of **20** and **21** with hydrogen and Pd/C in CH_3OH–EtOAc, respectively.

In summary, we have successfully developed a new method for the synthesis of shimofuridin analogs containing different nucleosides.

3. Experimental

3.1. General methods

Optical rotations were determined at 20 °C with a Perkin–Elmer model 241-Mc automatic polarimeter. Melting points were determined with a 'Mel-Temp' apparatus. ^1H and ^{13}C NMR spectra were recorded with Bruker ARX 400 spectrometers (400 MHz for ^1H, 100 MHz for ^{13}C) for solutions in $CDCl_3$ or CD_3OD as indicated. Chemical shifts are given in ppm downfield from internal Me_4Si. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector. Column chromatography was conducted by elution of a column (16 × 240, 18 × 300, 35 × 400 mm) of silica gel (100–200 mesh) with EtOAc–petroleum ether (60–90 °C) as the eluent. Solutions were concentrated at < 60 °C under reduced pressure.



Scheme 3. Reagents and conditions: (a) TMSOTf (0.5 equiv), CH_2Cl_2, rt, 2 h, 88% for **20**, 90% for **21**; (b) H_2, Pd/C 10%, 1:1 CH_3OH–EtOAc, rt, 24 h, 95% for **2**, 93% for **3**.

3.2. Methyl 5-*O*-benzoyl-α-D-arabinofuranoside (5)

To a stirred solution of **4** (7.86 g, 47.9 mmol) in dry Py (100 mL) was added dropwise a solution of BzCl (5.6 mL, 48 mmol) in dry CH_2Cl_2 (30 mL) at −5 °C over 30 min. After 2.5 h, the mixture was poured into ice-cold water and extracted with CH_2Cl_2 (200 mL). The organic layer was washed with 1N HCl (4 × 50 mL) and satd aq $NaHCO_3$ (30 mL), and then dried (Na_2SO_4). The extract was concentrated, and chromatographed on silica gel with 1:1 petroleum ether–EtOAc to give **5** as a syrup (7.70 g, 60); $[\alpha]_D^{20}$ +67° (*c* 4.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.09–8.00 (m, 2 H, Ph–*H*), 7.60–7.36 (m, 3 H, Ph–*H*), 4.90 (s, 1 H, H-1), 4.54 (dd, 1 H, $J_{4,5}$ 4.6, $J_{5,5'}$ 12.4 Hz, H-5), 4.51 (dd, 1 H, $J_{4',5'}$ 3.2, $J_{5,5'}$ 12.4 Hz, H-5′), 4.28 (dd, 1 H, $J_{2,3}$ 2.0, $J_{3,4}$ 6.2 Hz, H-3), 4.14 (d, 1 H, $J_{2,3}$ 2.0 Hz, H-2), 4.02 (m, 1 H, H-4), 3.39 (s, 3 H, OCH_3). Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.34; H, 5.95.

3.3. 5-*O*-Preparation of 5-*O*-benzoyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (6)

A solution of **5** (5.24 g, 19.5 mmol) in dry C_3H_6O containing 1% HCl (100 mL) was stored for 24 h at room temperature (rt). The mixture was neutralized with satd aq $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was crystallized from petroleum ether–EtOAc to give **6** (3.44 g, 60%). The remaining syrup was subjected to column chromatography with 2:1 petroleum ether–EtOAc as the eluent to afford additional **6** (0.86 g, 15%); mp 147.2–148.7 °C; $[\alpha]_D^{20}$ +22.6° (*c* 2.1, $CHCl_3$), [8]Lit. mp 147.5–148.5 °C; $[\alpha]_D$ +25.25° (*c* 0.079, $CHCl_3$).

3.4. 3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-arabinofuranose (7)

To a solution of **6** (3.8 g, 12.9 mmol) in dry $C_6H_5CH_3$ (100 mL) was added BnCl (4.5 mL, 50 mmol) and powdered KOH (4.2 g, 75 mmol) at rt. This mixture was heated under reflux with stirring for 5 h, at the end of which time TLC (4:1 petroleum ether–EtOAc) indicated that the reaction was complete. The mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4), concentrated and chromatographed on silica gel with 4:1 petroleum ether–EtOAc to give **7** as a syrup (4.06 g, 85%); $[\alpha]_D^{20}$ +13.2° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.31 (m, 10 H, 2 Ph*H*), 5.89 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.64 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), 4.60–4.54 (m, 4 H, 2 PhCH_2), 4.26 (m, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 6.3 Hz, H-4), 4.02 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 3.63 (d, 2 H, $J_{4,5}$ 6.3 Hz, H-5), 1.41, 1.33 (2 s, 6 H, 2 CCH_3). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.45; H, 7.01.

3.5. 1-(3,5-Di-*O*-benzyl-β-D-ribofuranosyl)thymine (9)

To a stirred solution of *O*,*O*-bis-(trimethylsilyl)thymine (0.44 g, 1.44 mmol) in dry CH_2Cl_2 (10 mL) with molecular sieves (4 Å, 0.7 g) was added a solution of 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**8**)[6] (0.3 g, 0.96 mmol) in dry CH_2Cl_2 (10 mL) at rt. After 8 h, HCOOH (0.5 mL) was added. After further 10 min, the mixture was diluted with CH_2Cl_2 (80 mL), washed with satd aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and then concentrated. The residue was chromatographed on silica gel with 1:2 petroleum ether–EtOAc to give **9** as white needles (0.37 g, 87%); mp 74–76 °C; $[\alpha]_D^{20}$ +26.5° (*c* 2.4, $CHCl_3$): ^{1}H NMR ($CDCl_3$): δ 9.42 (s, 1 H, N–*H*), 7.52 (s, 1 H, H-6), 7.40–7.21 (m, 10 H, 2 Ph*H*), 5.97 (d, 1 H, $J_{1',2'}$ 4.0, H-1′), 4.72, 4.59 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.53 (s, 2 H, PhCH_2), 4.33–4.23 (m, 2 H, H-3′, 4′), 4.12 (t, 1 H, $J_{1',2'}$ 4.0 Hz, $J_{2',3'}$ 4.0 Hz, H-2′), 3.83 (2 d, 1 H, $J_{4',5a'}$ 2.4, $J_{5a',5b'}$ 10.4 Hz, H-5a′), 3.68 (2 d, 1 H, $J_{4',5b'}$ 1.9, $J_{5a',5b'}$ 10.4 Hz, H-5b′), 3.15 (bs, 1 H, O*H*), 1.52 (s, 3 H, CH_3). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98. Found: C, 65.70; H, 6.01.

3.6. Preparation of 1-(3,5-di-*O*-benzyl-β-D-ribofuranosyl)uracil (10)

To a stirred solution of *O*,*O*-bis-(trimethylsilyl)uracil (241 mg, 0.85 mmol) in dry CH_2Cl_2 (8 mL) with molecular sieves (4 Å, 0.8 g) was added a solution of 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**8**)[6] (185 mg, 0.57 mmol) in dry CH_2Cl_2 (6 mL) at rt. After 8 h, HCOOH (0.5 mL) was added. After further 10 min, the mixture was diluted with CH_2Cl_2 (60 mL), washed with satd aq $NaHCO_3$ (10 mL), dried (Na_2SO_4), and then concentrated. The residue was chromatographed on silica gel with 1:2 petroleum ether–EtOAc to give **10** as white needles (202 mg, 85%); mp 69.8–71.5 °C; $[\alpha]_D^{20}$ +31.2° (*c* 2.1, $CHCl_3$), Lit.[6] mp 70–72 °C; $[\alpha]_D$ +31.7° (*c* 2.1, $CHCl_3$).

3.7. 2-(2,3,4-Tri-*O*-acetyl-β-L-fucopyranosylsulfanyl)-pyrimidine (12)

To a mixture of glycosl bromide **11**[10] (5.1 g, 14.4 mmol), 2-mercaptopyridine (4.86 g, 43.3 mmol), and Bu_4HSO_4 (4.9 g, 14.4 mmol) in CH_2Cl_2 (100 mL) was added 1 M aq Na_2CO_3 (100 mL). The mixture was stirred at rt for 1 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The mixture was partitioned between CH_2Cl_2 and water, the organic layer was concentrated, and the crude product was chromatographed on silica gel with 2:1 petroleum ether–EtOAc to give **12** as crystals (5.3 g, 96%); mp 102–103 °C; $[\alpha]_D^{20}$ −76° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.56 (d, 2 H, *J* 4.9 Hz, Pyr*H*-4, 6), 7.06 (t, 1 H, *J* 4.9 Hz, Pyr*H*-5), 5.82 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 5.43 (t, 1 H, $J_{1,2}$ 10.3 Hz, $J_{2,3}$ 10.3, H-2), 5.35 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-4), 5.19 (dd, 1 H, $J_{3,4}$ 3.4, $J_{2,3}$ 10.3 Hz, H-3), 4.03 (m, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 2.23, 2.04, 2.01 (3 s, 9 H, 3 COC H_3), 1.22 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6). Anal. Calcd for $C_{16}H_{20}N_2O_7S$: C, 49.99; H, 5.24. Found: C, 50.09; H, 5.23.

3.8. 2-(β-L-Fucopyranosylsulfanyl)pyrimidine (13)

To a solution of **12** (4.8 g, 12.5 mmol) in MeOH (50 mL) was added NaOMe (11 mg, 0.2 mmol). After 3 h at rt, TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated to afford **13** as crystals (3.24 g, quant): mp 152–154 °C; $[\alpha]_D^{20}$ 31° (*c* 4.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.46 (d, 2 H, *J* 4.7 Hz, Pyr*H*-4, 6), 7.10 (t, 1 H, *J* 4.7 Hz, Pyr*H*-5), 5.35 (d, 1 H, $J_{1,2}$ 10 Hz, H-1), 3.80 (m, 1 H, $J_{5,6}$ 9.2 Hz, H-5), 3.70–3.55 (m, 3 H, H-2, 3, 4), 1.10 (d, 3 H, $J_{5,6}$ 9.2 Hz, H-6). Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46. Found: C, 46.48; H, 5.41.

3.9. 2-(3,4-*O*-Isopropylidene-β-L-fucopyranosylsulfanyl)pyrimidine (14)

A mixture of **13** (2.8 g, 10.8 mmol), 2,2-dimethoxypropane (8 mL), and *p*-toluenesulfonic acid monohydrate (20 mg) in C_3H_6O (8 mL) was stirred for 20 h at rt, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was diluted with CH_2Cl_2, neutralized with satd aq $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel with 2:1 petroleum ether–EtOAc to give **14** as crystals (2.62 g, 81%); mp 91–93 °C; $[\alpha]_D^{20}$ −16.2° (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.55 (d, 2 H, *J* 4.8 Hz, Pyr*H*-4, 6), 7.02 (t, 1 H, *J* 4.8 Hz, Pyr*H*-5), 5.56 (d, 1 H, $J_{1,2}$ 10.3, H-1), 4.22–4.01 (m, 3 H, H-3, 4, 5), 3.82 (dd, 1 H, $J_{1,2}$ 10.3 Hz, $J_{2,3}$ 6.6 Hz, H-2), 3.30 (bs, 1 H, O*H*), 1.60, 1.40 (2 s, 6 H, 2 CCH_3), 1.38 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6). Anal. Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08. Found: C, 52.39; H, 6.01.

3.10. 2-(2-*O*-Benzyl-3,4-*O*-isopropylidene-β-L-fucopyranosylsulfanyl)pyrimidine (15)

To a solution of **14** (2.1 g, 7.04 mmol) in dry DMF (40 mL) was added slowly NaH (0.63 g, 80% in oil, 21 mmol), and then BnBr (0.68 mL, 7.74 mmol) at 0 °C. The mixture was stirred at rt for 5 h, at the end of which time TLC (4:1 petroleum ether–EtOAc) indicated that the reaction was complete. The mixture was poured into water, extracted repeatedly with CH_2Cl_2, and then concentrated. The residue was chromatographed on silica gel with 4:1 petroleum ether–EtOAc to afford **15** as crystals (2.4 g, 87%); mp

81–82 °C; $[\alpha]_D^{20}$ −34.6° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.52 (d, 2 H, *J* 4.7 Hz, Pyr*H*-4, 6), 7.40–7.23 (m, 5 H, Ph*H*), 6.96 (t, 1 H, *J* 4.6 Hz, Pyr*H*-5), 5.68 (d, 1 H, $J_{1,2}$ 9.3 Hz, H-1), 4.84, 4.78 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.33 (t, 1 H, $J_{2,3}$ 6.2, $J_{3,4}$ 6.2 Hz, H-3), 4.14–4.0 (m, 2 H, H-4, 5), 3.70 (d, 1 H, $J_{1,2}$ 9.3 Hz, $J_{2,3}$ 6.2 Hz, H-2), 1.52, 1.38 (2 s, 6 H, 2 CCH_3), 1.38 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6). Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.83; H, 6.23. Found: C, 61.90; H, 6.26.

3.11. 2-(2-*O*-Benzyl-β-L-fucopyranosylsulfanyl)-pyrimidine (16)

To a solution of **15** (1.6 g, 4.1 mmol) in anhyd MeOH (80 mL) was added a drop of H_2SO_4. The solution was stored at rt for 20 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was neutralized with satd aq $NaHCO_3$, and then concentrated. The residue was chromatographed on silica gel with 1:1 petroleum ether–EtOAc to give **16** as crystals (1.29 g, 90%); mp 113–115 °C; $[\alpha]_D^{20}$ −29° (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.55 (d, 2 H, *J* 4.8 Hz, Pyr*H*-4, 6), 7.40–7.22 (m, 5 H, Ph*H*), 7.00 (t, 1 H, *J* 4.8 Hz, Pyr*H*-5), 5.35 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 4.90, 4.78 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 3.95–3.70 (m, 4 H, H-2, 3, 4, 5), 1.35 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79. Found: C, 58.70; H, 5.80.

3.12. 2-(2-*O*-Benzyl-3,4-*O*-isopropylidene-β-L-fucopyranosylsulfanyl)pyrimidine (17)

To a solution of **16** (1.2 g, 3.4 mmol) in MeOH (50 mL) was added Bu_2SnO (845 mg, 3.4 mmol), and the mixture was heated at reflux. After the mixture became clear, heating was continued for 1 h, and the stannylene complex was obtained as a white foamy residue by evaporation of the MeOH under diminished pressure. To the residue was added $C_6H_5CH_3$ (30 mL), tetrabutylammonium iodide (1.26 g, 3.4 mmol), and BnBr (0.4 mL, 3.7 mmol). The mixture was stirred at 50 °C for 18 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solvent was evaporated under diminished pressure, and the residue was subjected to column chromatography on silica gel with 2:1 petroleum ether–EtOAc as the eluent to afford **17** as a syrup (1.06 g, 71%); $[\alpha]_D^{20}$ −19° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.55 (d, 2 H, *J* 4.9 Hz, Pyr*H*-4, 6), 7.43–7.21 (m, 10 H, 2 Ph*H*), 7.01 (t, 1 H, *J* 4.9 Hz, Pyr*H*-5), 5.36 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 4.83 (s, 2 H, PhCH_2), 4.78, 7.75 (2 d, 2 H, *J* 12.2 Hz, PhCH_2), 4.08 (t, 1 H, $J_{1,2}$ 10.0, $J_{2,3}$ 10.0 Hz, H-2), 3.86 (d, 1 H, $J_{3,4}$ 3.9 Hz, H-4), 3.73 (q, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 3.66 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.9 Hz, H-3), 2.71 (bs, 1 H, O*H*), 1.36 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6). Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98. Found: C, 65.80; H, 5.99.

3.13. 2-(2,3-Di-*O*-benzyl-4-*O*-stearoyl-β-L-fucopyranosylsulfanyl)pyrimidine (18)

Stearoylation of **17** (0.4 g, 0.91 mmol) with stearoyl chloride (0.45 g, 1.5 mmol) in Py (8 mL) at rt for 3 h gave compound **18** as a syrup (0.58 g, 90%); $[\alpha]_D^{20}$ −46° (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.52 (d, 2 H, *J* 4.8 Hz, Pyr–*H*-4, 6), 7.38–7.20 (m, 10 H, 2 Ph*H*), 6.98 (t, 1 H, *J* 4.8 Hz, Pyr*H*-5), 5.68 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 5.45 (d, 1 H, $J_{3,4}$ 2.0 Hz, H-4), 4.82 (s, 2 H, PhCH_2), 4.76, 4.55 (2 d, 2 H, *J* 11.2 Hz, PhCH_2), 3.95–3.70 (m, 3 H, H-2, 3, 5), 2.48 (t, 2 H, *J* 6.2 Hz, COCH_2C$_{16}$H$_{33}$), 1.72–1.60 (m, 2 H, COCH$_2$CH_2C$_{15}$H$_{31}$), 1.48–1.06 (m, 31 H, COCH$_2$CH$_2$C$_{14}$$H_{28}CH_3$, H-6), 0.9 (t, 3 H, *J* 4.5 Hz, COC$_{16}$H$_{32}$CH_3). Anal. Calcd for $C_{42}H_{60}N_2O_5S$: C, 71.55; H, 8.58. Found: C, 71.51; H, 8.50.

3.14. 2-(4-*O*-Acetyl-2,3-di-*O*-benzyl-β-L-fucopyranosylsulfanyl)pyrimidine (19)

Acetylation of **17** (100 mg, 0.23 mmol) with Ac_2O (4 mL) in Py (5 mL) at rt for 2 h gave **19** as a syrup (106 mg, 97%); $[\alpha]_D^{20}$ −5° (*c* 3.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8. 52 (d, 2 H, *J* 4.8 Hz, Pyr*H*-4, 6), 7.40–7.18 (m, 10 H, 2 Ph*H*), 6.98 (t, 1 H, *J* 4.8 Hz, Pyr*H*-5), 5.70 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 5.44 (d, 1 H, $J_{3,4}$ 1.7 Hz, H-4), 4.83 (s, 2 H, PhCH_2), 4.77, 4.55 (2 d, 2 H, *J* 11.2 Hz, PhCH_2), 3.94–3.75 (m, 3 H, H-2, 3, 5), 2.20 (s, 3 H, COCH_3), 1.22 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6). Anal. Calcd for $C_{26}H_{28}N_2O_5S$: C, 64.98; H, 5.87. Found: C, 65.09; H, 5.85.

3.15. 3′,5′-Di-*O*-benzyl-2′-*O*-(2,3-di-*O*-benzyl-4-*O*-stearoyl-α-L-fucopyranosyl)thymidine (20)

To a stirred solution of **18** (200 mg, 0.28 mmol) and **9** (124.4 mg, 0.28 mmol) in dry CH_2Cl_2 (15 mL) was added TMSOTf (27 μL, 0.14 mmol) at rt. After 3 h, Et_3N was added to the solution to quench the reaction. The solution was concentrated, and chromatographed on a silica gel column with 1:1 petroleum ether–EtOAc to give **20** (254 mg, 88%) as a syrup; $[\alpha]_D^{20}$ −2.1° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.30 (s, 1 H, N-*H*), 7.70 (s, 1 H, H-6), 7.40–7.18 (m, 20 H, 4 Ph*H*), 6.04 (d, 1 H, $J_{1',2'}$ 6.7 Hz, H-1′), 5.42 (d, 1 H, $J_{3'',4''}$ 3.0 Hz, H-4″), 5.30 (d, 1 H, $J_{1'',2''}$ 3.3 Hz, H-1″), 4.80–4.45 (m, 8 H, 4 PhCH_2), 4.40 (t, 1 H, $J_{1',2'}$ 6.7, $J_{2',3'}$ 2.7 Hz, H-2′), 4.35 (dd, 1 H, $J_{2',3'}$ 2.7 Hz, $J_{3',4'}$ 3.0 Hz, H-3′), 4.25 (q, 1 H, $J_{5'',6''}$ 6.6 Hz, H-5″), 4.15 (m, 1 H, $J_{3',4'}$ 3.0, $J_{4',5a'}$ 3.0, $J_{4',5b'}$ 2.0 Hz, H-4′), 4.0 (dd, 1 H, $J_{2'',3''}$ 10.0 Hz, $J_{3'',4''}$ 3.0 Hz, H-3″), 3.92 (2 d, 1 H, $J_{4',5a'}$ 3.0, $J_{5a',5b'}$ 12.0 Hz, H-5a′), 3.80 (dd, 1 H, $J_{1'',2''}$ 3.3 Hz, $J_{2'',3''}$ 10.0 Hz, H-2″),

3.65 (2 d, 1 H, $J_{4',5b'}$ 2.0, $J_{5a',5b'}$ 12.0 Hz, H-5b′), 2.36 (t, 2 H, J 6.2 Hz, $COCH_2C_{16}H_{33}$), 1.62 (m, 2 H, $COCH_2CH_2C_{15}H_{31}$), 1.50 (s, 3 H, C_5-CH_3), 1.36–1.16 (m, 28 H, $COCH_2CH_2C_{14}H_{28}CH_3$), 1.13 (d, 3 H, $J_{5'',6''}$ 6.6 Hz, H-6″), 0.90 (t, 3 H, J 4.5 Hz, $COC_{16}H_{32}CH_3$). Anal. Calcd for $C_{62}H_{82}N_2O_{11}$: C, 72.20; H, 8.01. Found: C, 72.40; H, 7.92.

3.16. 2′-*O*-(4-*O*-Stearoyl-α-L-fucopyranosyl)thymidine (2)

A suspension of Pd/C (10%, 150 mg) in a solution of **20** (110 mg, 0.107 mmol) in 1:1 CH_3OH–EtOAc (15 mL) was stirred under a flow of H_2 at 1 atm and rt for 24 h, then filtered and concentrated. Column chromatography of the residue on Bio-Gel P-4 with CH_3OH as the eluent gave, after freeze drying, **2** (68 mg, 95%); $[\alpha]_D^{20}$ −5.4° (*c* 0.7, MeOH); ^{1}H NMR (CD_3OD): δ 8.80 (br s, 1 H, N–*H*), 7.81 (s, 1 H, H-6), 6.15 (d, 1 H, $J_{1',2'}$ 6.2 Hz, H-1′), 5.15 (d, 1 H, $J_{3'',4''}$ 3.6 Hz, H-4″), 5.05 (d, 1 H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.90 (dd, 1 H, $J_{1',2'}$ 6.2, $J_{,3'}$ 4.7 Hz, H-2′), 4.50 (dd, 1 H, $J_{2',3'}$ 4.7, $J_{3',4'}$ 2.6 Hz, H-3′), 4.22 (m, 1 H, H-4′), 3.98 (dd, 1 H, $J_{2'',3''}$ 9.9 Hz, $J_{3'',4''}$ 3.5 Hz, H-3″), 3.85 (m, 1 H, H-5a′), 3.78 (m, 1 H, H-5b′), 3.76 (dd, 1 H, $J_{1'',2''}$ 3.6, $J_{2'',3''}$ 9.9, H-2″), 3.68 (q, 1 H, $J_{4'',5''}$ 3.0, $J_{5'',6''}$ 6.2 Hz, H-5″), 2.40–0.8 (35 H, $COC_{17}H_{35}$), 1.46 (s, 3 H, C_5–CH_3), 0.68 (d, 3 H, $J_{5'',6''}$ 6.2 Hz, 3 H-6″). Anal. Calcd for $C_{34}H_{58}N_2O_{11}$: C, 60.88; H, 8.71. Found: C, 60.85; H, 8.76.

3.17. 3′,5′-Di-*O*-benzyl-2′-*O*-(2,3-di-*O*-benzyl-4-*O*-stearoyl-α-L-fucopyranosyl)uridine (21)

To a stirred solution of **18** (112 mg, 0.16 mmol) and **10** (67.4 mg, 0.16 mmol) in dry CH_2Cl_2 (12 mL) was added TMSOTf (15 μL, 0.08 mmol) at rt. After 3 h, Et_3N was added to the solution to quench the reaction. The solution was concentrated, and chromatographed on silica gel column with 1:1 petroleum ether–EtOAc to give **21** (146.5 mg, 90%) as a syrup; $[\alpha]_D^{20}$ −3.2° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 1 H, N–*H*), 7.8 (d, 1H, $J_{5,6}$ 8.1 Hz, H-6), 7.40–7.20 (m, 20 H, 4 Ph*H*), 5.98 (d, 1 H, $J_{1',2'}$ 6.4 Hz, H-1′), 5.39 (d, 1 H, $J_{3'',4''}$ 2.7 Hz, H-4″), 5.33 (d, 1 H, $J_{1'',2''}$ 3.6 Hz, H-1″), 5.21 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-5), 4.75–4.41 (m, 8 H, 4 $PhCH_2$), 4.38–4.28 (m, 2 H, H-2′, 3′), 4.21 (q, $J_{5'',6''}$ 6.5 Hz, H-5″), 4.10 (m, 1 H, H-4′), 3.99 (dd, 1 H, $J_{2'',3''}$ 10.0, $J_{3'',4''}$ 2.7 Hz, H-3″), 3.89 (2 d, 1 H, $J_{4',5'}$ 2.4, $J_{5'a,5'b}$ 10.4 Hz, H-5a′), 3.81 (dd, 1 H, $J_{1'',2''}$ 3.6, $J_{2'',3''}$ 10.0 Hz, H-2″), 3.68 (dd, 1 H, $J_{4',5b'}$ 1.7, $J_{5'a,5'b}$ 10.0 Hz, H-5b′), 2.38 (t, 2 H, J 6.4 Hz, $COCH_2C_{16}H_{33}$), 1.60 (m, 2 H, $COCH_2CH_2C_{15}H_{31}$), 1.36–1.1.8 (m, 28 H, $COC_2H_4C_{14}H_{28}CH_3$), 1.11 (d, 3 H, $J_{5'',6''}$ 6.7 Hz, H-6″), 0.87 (t, 3 H, J 7.0 Hz, $COC_{16}H_{32}CH_3$). Anal. Calcd for $C_{61}H_{80}N_2O_{11}$: C, 72.02; H, 7.93. Found: C, 72.19; H, 7.90.

3.18. 2′-*O*-(4-*O*-Stearoyl-α-L-fucopyranosyl)uridine (3)

Debenzylation of **21** (63 mg, 0.06 mmol) as described for the debenzylation of **20** gave **3** (37.8 mg, 93%); $[\alpha]_D^{20}$ −6.3° (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$): δ 8.77 (s, 1 H, N–*H*), 7.88 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 6.08 (d, 1 H, $J_{1',2'}$ 6.3, H-1′), 5.18 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 5.13 (d, 1 H, $J_{3'',4''}$ 2.8 Hz, H-4″), 5.03 (d, 1 H, $J_{1'',2''}$ 3.2 Hz, H-1″), 4.87 (dd, 1 H, $J_{1',2'}$ 6.3 Hz, $J_{2',3'}$ 4.5 Hz, H-2′), 4.53 (dd, 1 H, $J_{2',3'}$ 4.5, $J_{3',4'}$ 2.8 Hz, H-3′), 4.26 (m, 1 H, H-4′), 3.91 (dd, 1 H, $J_{2'',3''}$ 9.5, $J_{3'',4''}$ 3.6 Hz, H-3″), 3.82 (m, 1 H, H-5a′), 3.79 (1 H, m, H-5b′), 3.73 (dd, 1 H, $J_{1'',2''}$ 3.2 Hz, $J_{2'',3''}$ 9.5 Hz, H-2″), 3.64 (q, 1 H, $J_{4'',5''}$ 2.8, $J_{5'',6''}$ 6.6 Hz, H-5″), 2.37–0.82 (35 H, $COC_{17}H_{35}$), 0.66 (d, 3 H, $J_{5'',6''}$ 6.6 Hz, H-6″). Anal. Calcd for $C_{33}H_{56}N_2O_{11}$: C, 60.35; H, 8.59. Found: C, 60.41; H, 8.63.

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