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SYNTHESIS OF 2'-*O*-[(4''-*O*-STEAROYL)-α-L-FUCOPYRANOSYL]THYMIDINE: A SHIMOFURIDIN ANALOGUE

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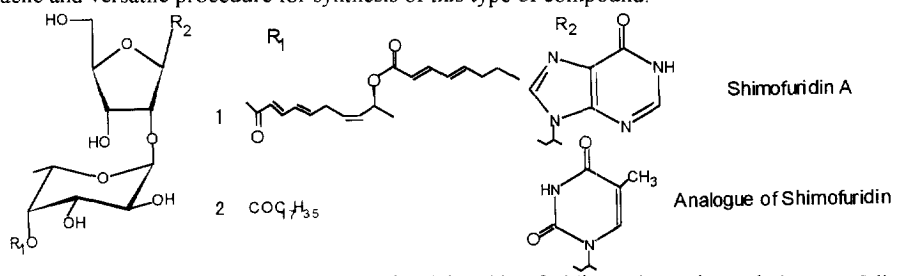
Abstract: A synthesis of the title compound has been achieved. The procedure involves a facile preparation of 1'-(3',5'-di-*O*-benzyl-ß-D-ribofuranosyl)-thymine (**8**) with 1,2-anhydroribofuranose (**7**) as the glycosyl donor, stereoselective formation of a 1,2-*cis* (α) interglycoside bond with 4-*O*-stearoylated pyrimidin-2-yl 1 thio-β-L-fucopyranoside (**16**) as the glycosyl donor. © 1997 Elsevier Science Ltd.

Kobayashi et al[1] showed that 2'-*O*-[(4''-*O*-(9'''-*O*-octadienoyl)-decatrienoyl)-α-L-fucopyranosyl]inosine (**1**), so called Shimofuridin A, a nucleoside derivative exhibiting cytotoxic and antimicrobial activities, occurred in the extract of the Okinawa Marine tunicate *Aplidium multiplicatum* Sluiter. Later on, the structure of six new nucleoside derivatives (*i.e.*Shimofuridins B-G), isolated from the same tunicate, was elucidated[2]. Shimofuridins B-E are stereoisomers of Shimofuridin A (**1**) as to the geometry of the double bonds in the unsaturated acyl chain moieties, while Shimofuridins F and G possess homologous acyl chains with two more carbon units.

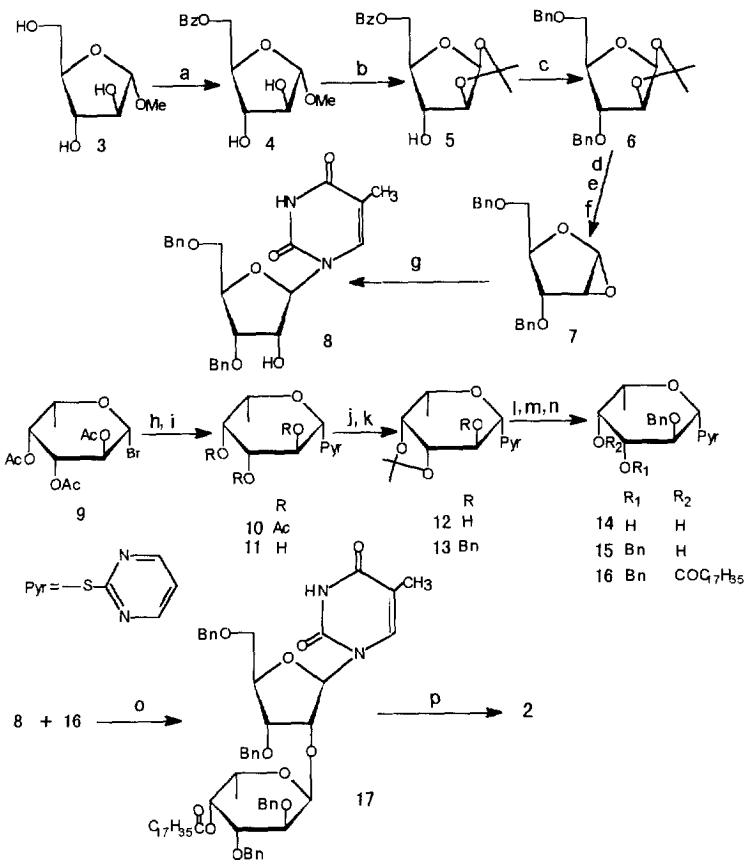
In 1996, van Boom's and Spencer Knapp's groups reported studies on the synthesis of Shimofuridin analogs respectively[3,4]. Here we report a different approach to the preparation of the 2'-*O*-[(4''-*O*-stearoyl)-α-L-fucopyranosyl]-thymidine (**2**) based on the properly protected units 1,2-anhydroribofuranose **7**, activated thymine and pyrimidin-2-yl 1-thio-ß-L-fucopyranoside **16**, demonstrating a new facile and versatile procedure for synthesis of this type of compound.



As shown in the scheme, the synthesis of the Shimofuridin analogue is carried out as following.

Benzoylation of methyl-D-arabinofuranoside[5] (**3**) with benzoyl chloride in pyridine selectively afforded methyl 5-*O*-benzoyl-D-arabinofuranoside (**4**) in 60% yield, which was then converted to 1,2-*O*-isopropylidene-5-*O*-benzoyl- β -D-arabinofuranose (**5**) in acetone containing dry hydrogen chloride in

Scheme



Reagents and conditions: (a) BzCl (1.0 equiv.), pyridine, -5°C, 4h, 60%. (b) acetone/dry HCl, RT., 24 h, 75%. (c) BnCl (2.2 equiv.)/toluene/KOH, reflux, 5h. 85%. (d) 30% AcOH, reflux, 3h, 95%. (e) TsCl (2.0 equiv.), pyridine, RT, 15h, 75%. (f) potassium *tert*-butoxide (1.1 equiv.), THF, RT, 20 min, 95%. (g) trimethylsilylated thymine (1.5 equiv.), CH_2Cl_2, RT, 12 h, 87%. (h) 2-mercaptopyrimidine (1.5 equiv.), tetrabutylammonium hydrogensulfate, Na_2CO_3, CH_2Cl_2-H_2O, RT, 12h, 96%. (i) CH_3OH/catalytic amount $NaOCH_3$, RT, 1h, 100%. (j) $Me_2C(OMe)_2$/acetone, catalytic amount TsOH, RT, 10h, 81%. (k) BnBr, NaH, TMF, reflux, 5h, 87%. (l) CH_3OH/H_2SO_4, RT, 20 h, 97%. (m) CH_3OH/dibutyltin oxide; toluene/tetrabutylammonium iodide/BnBr, 71%. (n) $C_{17}H_{35}COCl$, pyridine, RT, 1h, 90%. (o) **8** (1.4 equiv.). TMSOTf (0.4 equiv), CH_2Cl_2, RT, 5h, 90%. (p) H_2, Pd/C 10%, EtOAc, RT, 1h, 100%.

75% yield. Benzylation of **5** with benzyl chloride in anhydrous toluene containing potassium hydroxide gave the known compound[6] **6** in 85% yield. which was smoothly converted to the 1,2-anhydro-3,5-di-*O*-benzyl- α -D-ribofuranose (**7**) (67% for three steps) according to the method developed in our lab[6]. The procedure for the preparation of compound **6** described here with 5-*O*-benzoate of arabinofuranoside (**4**) as the key

intermediate instead of the corresponding 5-*O*-tosylate[7] is more simple and easily operational and this makes the synthesis of compound **7** from D-arabinose as the starting material in large scale more practical. Reaction of **7** with trimethylsilylated thymine in the absence of Lewis acid provided the key intermediate **8** in 87% yield.

Treatment of the acetobromosugar[8] **9** with 2-mercaptopyrimidine, tetrabutylammonium hydrogensulfate, and sodium carbonate in a mixture of dichloromethane and water under phase-transfer conditions[9] at room temperature afforded the fully acetylated pyrimidin-2-yl 1-thio-L-fucopyranoside (**10**) in 96% yield. Deacetylation of **10** with catalytic amount of sodium methoxide in methanol gave the compound **11**, which was then treated with 2,2-dimethoxypropane in the presence of a catalytic amount *p*-toluenesulfonic acid in acetone to give 3,4-*O*-isopropylidene-pyrimidin-2-yl 1-thio-L-fucopyranoside (**12**) in 81% yield (for two steps). Benzylation of **12** with benzyl bromide and sodium hydride in N,N-dimethylformamide followed by hydrolysis in methanol containing a catalytic amount sulfuric acid gave the compound **14** in 84% yield (for two steps). Selective benzylation of pyrimidin-2-yl 2-*O*-benzyl-1-thio-ß-L-fucopyranoside (**14**) with benzylbromide *via* dibutyltin complex gave **15** in 71% yield. Stearoylation of **15** with $C_{17}H_{34}COCl$ in pyridine gave the another key intermediate pyrimidin-2-yl 2,3-di-*O*-benzyl-4-*O*-stearoyl-1-thio-ß-L fucopyranoside (**16**) in 90% yield.

We are gratified to find that condensation of **8** with the acceptor **16** in dichloromethane at room temperature in the presence of TMSOTf (0.5 equiv.) afforded the blocked target compound (α-linked **17**) as the sole product in 90% yield (based on **16**). The chemical shift δ 5.30 for H-1'' definitely indicated α configuration of fucoside linkage[3]. The use of pyrimidin-2-yl 1-thio-ß-L-fucopyranoside as glycosyl donor showed some advantages since the 1-thio-pyrimidine was stable enough allowing chemical modification at 2-, 3-, or 4-hydroxy group of the fucopyranoside, and also active enough as a leaving group for high yield coupling with the nucleoside acceptor in the presence of small amount TMSOTf. Further application of pyrimidine-2-yl 1-thio-fucopyranoside as the glycosyl donor for construction of oligosaccharides is under investigation. The title compound **2** was obtained by catalytic debenzylation of **17** with hydrogen and Pd/C in EtOAc quantitatively. All of the new compounds involved in the present research were characterized by ^1H or ^{13}C NMR spectrometry[11], elemental analysis, and optical rotation. It is noted that Fraser-Reid's group reported a new method for debenzylation with $FeCl_3$ in CH_2Cl_2 indicating that allyl, acetyl, alkene, etc groups were not effected[10]. This would provide an alternative way for debenzylation in the preparation of other Shimofuridin analogues with alkene side chains.

In summary, we have successfully developed a versatile procedure for the synthesis of a Shimofuridin analogue, and the synthetic pathway presented here opens a way to the future synthesis of Shimofuridins and their analogs.

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11 All new compounds gave satisfactory elemental analysis results. Selected ^{1}H NMR ($CDCl_3$, Me_4Si as internal standard) data are as follows: **4**. 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 Hz, $J_{5,5'}$ = 12.4 Hz, H-5), 4.51 (dd, 1 H, $J_{4,5'}$ = 3.2 Hz, $J_{5,5'}$ = 12.4 Hz, H-5'), 4.28 (dd, 1 H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 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). **8**. 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 Hz, H-1'), 4.72, 4.59 (ABq, 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, $J_{1',2'} = J_{2',3'}$ = 4.0 Hz, H-2'), 3.83 (2 d, 1 H, $J_{4',5a'}$ = 2.4 Hz, $J_{5a',5b'}$ = 10.4 Hz, H-5a'), 3.68 (2 d, 1 H, $J_{4',5b'}$ = 1.9 Hz, $J_{5a',5b'}$ = 10.4 Hz, H-5b'), 3.15 (bs, 1 H, O*H*), 1.52 (s, 3 H, CH_3). **16**. 8.52 (d, 2 H, J = 4.8 Hz, Pyr-*H*), 7.38-7.20 (m, 10 H. 2 Ph-*H*), 6.98 (t, 1 H, J = 4.8 Hz, Pyr-*H*), 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 (ABq, 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, COC$H_2C_{16}H_{33}$), 1.72-1.60 (m, 2 H, $COCH_2CH_2C_{15}H_{31}$), 1.48-1.06 (m, 31 H, $COCH_2CH_2C_{14}H_{28}CH_3$, H-6), 0.9 (t, 3 H, J = 4.5 Hz, $COC_{16}H_{32}CH_3$). **17**. 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, $J_{1',2'}$ = 2.7 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, $J_{1',2'} = J_{2',3'}$ = 2.7 Hz, H-2'), 4.35 (dd, $J_{2',3'}$ =2.7 Hz, $J_{3',4'}$ = 3.0 Hz, H-3'), 4.25 (q, $J_{5'',6''}$ = 6.6 Hz, H-5''), 4.15 (m, $J_{3',4'}$ = 3.0 Hz, $J_{4',5a'}$ = 3.0 Hz, $J_{4',5b'}$ = 2.0 Hz, H-4'), 4.0 (dd, $J_{2'',3''}$ = 10.0 Hz, $J_{3'',4''}$ = 3.0 Hz, H-3''), 3.92 (2d, 1 H, $J_{4',5a'}$ = 3.0 Hz, $J_{5a',5b'}$ = 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 Hz, $J_{5a',5b'}$ = 12.0 Hz, H-5b'), 2.36 (t, 2 H, J = 6.2 Hz, COC$H_2C_{16}H_{33}$), 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, $COC_{16}H_{32}CH_3$). $[\alpha]_D^{20}$ -2.1° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{62}H_{82}O_{11}N_2$: C, 72.32; H, 7.96. Found: C, 72.40; H, 7.92. **2**. ^{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, $J_{1'',2''}$ = 3.7 Hz, H-1''), 4.90 (1 H, dd, $J_{1',2'}$ = 6.2 Hz, $J_{2',3'}$ = 4.7 Hz, H-2'), 4.50 (1 H, dd, $J_{2',3'}$ = 4.7 Hz, $J_{3',4'}$ = 2.6 Hz, H-3'), 4.22 (1 H, m, H-4'), 3.98 (1 H, dd, $J_{2'',3''}$ = 9.9 Hz, $J_{3'',4''}$ = 3.5 Hz, H-3''), 3.85 (1 H, m, H-5a'), 3.78 (1 H, m, H-5b'), 3.76 (1 H, dd, $J_{1'',2''}$ = 3.6 Hz, $J_{2'',3''}$ = 9.9 Hz, H-2''), 3.68 (1 H, dq, $J_{4'',5''}$ = 3.0 Hz, $J_{5'',6''}$ = 6.2 Hz, H-5''), 2.40-0.8 (35 H, $COC_{17}H_{35}$), 0.68 (d, 3 H, $J_{5'',6''}$ = 6.2 Hz, H-6''). $[\alpha]_D^{20}$ -5.4° (*c* 0.7, MeOH). Anal. Calcd for $C_{34}H_{58}O_{11}N_2$: C, 60.89; H, 8.66. Found: C, 60.85; H, 8.71.

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