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An approach towards the synthesis of sialyl nucleoside mimetics

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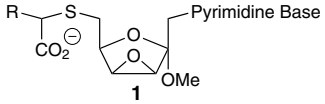
Abstract—An approach towards the synthesis of novel sialyl nucleoside mimetics based on D-fructose is described. The synthesis of these mimetics is achieved in good overall yield in seven steps. The key synthetic step is the coupling reaction of pyrimidine bases (uracil, 5-fluorouracil and cytosine) to the C-1 position of the modified D-tagatofructofuranoside.

1. Introduction

The role of carbohydrates and in particular sialic acids, and the malignancy of tumour cells is now evident.[1–7] The correlation between levels of sialylation and specific cancerous processes such as metastasis, can in principle be due to changes in the activities of a range of sialic acid metabolizing enzymes.

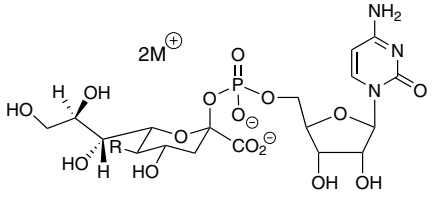


1

R = methyl, ethyl, phenyl

As part of our ongoing efforts to elucidate important recognition features required in the specific inhibition of sialic acid recognizing proteins in general, we have synthesized a range of sialyl nucleoside mimetics based on the very inexpensive carbohydrate D-fructose. Our ongoing interest in fructose chemistry[8] and the development of novel sialyl mimetics initiated our present investigation on the synthesis of sialyl mimetic nucleosides of the general structure **1**, which can be considered as mimetics of CMP-Neu5Ac **2**, or CMP-KDN **3**.

Our design concept towards the synthesis of compounds of the general structure **1** was to produce sialyl mimetics that retained the structural features essential for interactions with sialyl nucleotide-recognizing proteins, but may also possess improved pharmacological profiles. Functional group manipulations and glycosidation reactions of sialic acids and carbohydrate-based compounds in general are inherently difficult to successfully carry out. This fact has in part resulted in the current interest in the development of sialic acid mimetics.[9–12] As a consequence of this interest, there have been numerous sialyl mimetic studies that have validated such an approach. For example, sialyl mimetic inhibitors of sialidases[13–17] and sialyl mimetic inhibitors of sialyl transferases.[18,19]



CMP-Neu5Ac (R = NHAc) **2**
CMP-KDN (R = OH) **3**

2. Results and discussion

Inspection of the sialyl mimetic **1** in relation to naturally occurring substrates **2** and **3** shows that the sialic acid-phosphate portion has been replaced by a thio-linked carboxylate functionality associated with a variable group 'R'. This approach was adopted to explore the effects of replacing the entire sialic acid moiety with a group that maintains one of the charges present in the natural substrates. The variable 'R' group in **1** would allow an investigation into the effects of hydrophobicity,

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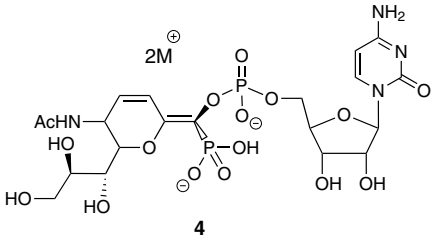
hydrophilicity and steric bulk for sialic acid recognizing proteins. While the carboxylate functionality in **1** is not maintained in the exact same relative position as the carboxylate group in **2** and **3**, it maintains a charged moiety in the same spacial location of the phosphate and carboxylate groups. This is not an unreasonable approach as reports exist indicating that the replacement of the entire sialic acid moiety by a carboxylate group gives an equivalent if not improved affinity for some proteins.[10]

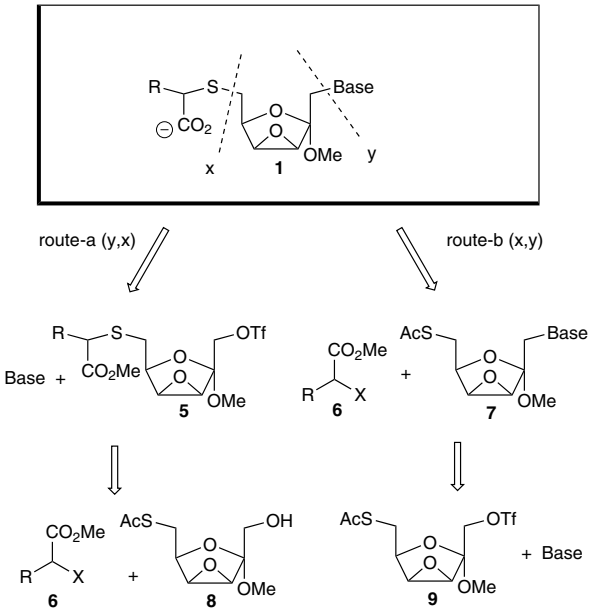
The sialyl transferase enzyme inhibitor KI-8110 **4** has a K_i = 40 nM, which is 1000 times greater in affinity than the natural substrate CMP-Neu5Ac **2**. While **4** mimics the natural substrate in possessing a phosphate linkage, this linkage is highly acid labile and was viewed as a feature that might advantageously be replaced. In an attempt to improve metabolic stability, we utilized some of our previous work[20] and incorporated the thio-linkage between the fructose and the sialic acid mimetic.



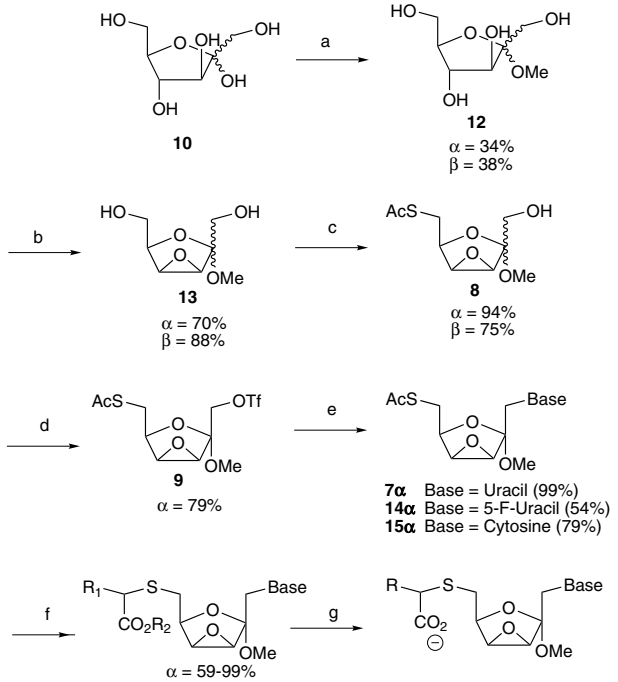
4

From a retrosynthetic viewpoint, there are two distinct pathways towards the sialyl mimetics of the general structure **1** (Scheme 1). The first approach (route-a) involves coupling the sialyl mimetic group to the fructose derivative followed by coupling of the pyrimidine base to the sialyl mimetic sugar. Alternatively, (route-b) the pyrimidine base could be coupled to the activated C-1 of the fructose derivative followed by coupling to the sialyl mimetic. We decided that the more attractive sequence would likely be route-a. We have routinely coupled thiolacetyl groups to sugars[21] and found them to be relatively robust functionalities in regard to their presence during other functional group transformations. We were more comfortable with the thiolacetyl group being present on the sugar, then proceeding with attempts at the previously unreported coupling of the pyrimidine base onto the C-1 secondary alcohol of the modified fructose.

Our overall approach to the formation of sialyl nucleoside mimetics **1** from readily available D-fructose **10** is detailed in Scheme 2, with the key step being the coupling of **9** to the pyrimidine base. To stabilize the anomeric configuration of D-fructose, the methyl glycoside of **10** was prepared via a Fischer type methodology[22] to give methyl β-D-fructopyranoside **11** (20%), **12α** (38%) and **12β** (34%) after separation on a Dowex (1 × 8-200, $^-$OH-form) resin. Although the C-1 and C-6 hydroxyls are known to be more reactive than C-3 and C-4,[8,23] we wanted to protect C3 and C4 in order to prevent any unwanted side reactions.



Scheme 1. Retrosynthetic approach towards sialyl mimetics of general structure **1**.



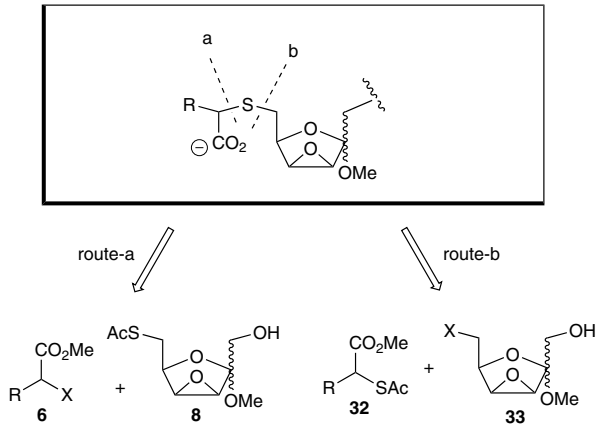
16 R_1 = methyl, R_2 = ethyl, Base = Uracil
17 R_1 = ethyl, R_2 = methyl, Base = Uracil
18 R_1 = phenyl, R_2 = methyl, Base = Uracil
19 R_1 = methyl, R_2 = ethyl, Base = 5-F-Uracil
20 R_1 = ethyl, R_2 = methyl, Base = 5-F-Uracil
21 R_1 = phenyl, R_2 = methyl, Base = 5-F-Uracil
22 R_1 = ethyl, R_2 = methyl, Base = Cytosine
23 R_1 = phenyl, R_2 = methyl, Base = Cytosine

24 R = methyl, Base = Uracil
25 R = ethyl, Base = Uracil
26 R = phenyl, Base = Uracil
27 R = methyl, Base = 5-F-Uracil
28 R = ethyl, Base = 5-F-Uracil
29 R = phenyl, Base = 5-F-Uracil
30 R = ethyl, Base = Cytosine
31 R = phenyl, Base = Cytosine

Scheme 2. Synthesis of sialyl mimetic nucleosides. Reagents and conditions: (a) MeOH, AcCl, rt, 16 h; (b) PPh_3, DIAD, DMF, rt, 40 h; (c) PPh_3, DIAD, AcSH, THF, 4 °C, 24 h; (d) Tf_2O, CH_2Cl_2, 0 °C, 1 h; (e) (i) HMDS, TMSCl, base, reflux, 16 h; (ii) **9**, 1,2-DCE, 60 °C, Ar, 2 days; (f) α-halo-ester, H_2NNH_2·AcOH, Et_3N, DMF, rt, 3.5 h; (g) 1 M NaOH, MeOH, rt, 16 h.

The 3,4-epoxidation reaction under Mitsunobu conditions[24–26] was performed in one-step in separate reactions on **12α** and **12β**, in relatively high yield, to give **13α** and **13β** following flash column chromatography. The presence of the 3,4-epoxide would allow for potential derivatization at later stages in the synthesis, although this was not explored in this study.

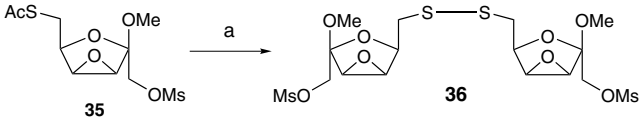
Retrosynthetically, the next step provided us with a further two distinct pathways towards obtaining the coupling of the sialyl mimetic to the derivatized D-fructose (Scheme 3). We either introduced the thiolacetyl group to form the derivatized fructose **8** before coupling with an α-halo-ester derivative (e.g., **6**) ('route-a'), or we coupled a C-6 activated fructose like **33** with an α-thiolacetyl carboxylate derivative **32** ('route-b'). A number of α-halo-ester derivatives are commercially available, and we therefore decided to take advantage of this and follow route-a.



Scheme 3. Retrosynthetic strategy towards **1**.

Utilizing the strategy of route-a and employing knowledge from our previous work on 3,4-anhydro-β-D-tagatofuranosides,[8] we were able to selectively thiolacetylate C-6 on **13** to give **8** in good yield for both the α- and β-anomers. Only minor amounts of the 1,6-di-SAc-functionalized materials, **34α** and **34β**, were formed in this reaction.

We decided to proceed with the α-anomer of **8** selectively in our remaining synthetic strategy, as it most closely resembled the configuration of CMP-Neu5Ac **2** and CMP-KDN **3**. In order to couple the pyrimidine base to the derivatized tagatofuranoside **8α**, requisite activation of the C-1 hydroxyl group was achieved by *O*-triflation[27] to give **9α**. The pyrimidine base was also activated via silylation using hexamethyldichlorosilizane (HMDS) and trimethylsilylchloride (TMSCl) to give the aromatized silylated base. The optimized coupling reaction between the activated sugar and base was found to proceed quite slowly, but respectable yields were obtained after several days stirring at 60 °C under Ar. Yields for the formation of **7α**, **14α** and **15α** after chromatography were 99%, 54% and 79% when the base was uracil, 5-fluorouracil and cytosine, respectively. With 5-fluorouracil as the base, co-elution between the product and uncoupled base was encountered in the chromatography purification process, requiring repeated chromatography steps and resulting in a low yield. This is a modified version of a method employed to synthesize anti-HIV 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides[28,29] and 5-fluoro-4′-thiouridinenucleosides.[30] These methods were employed to couple the base to the anomeric position of the sugar, a much more reactive position than the primary carbon in this work. Therefore, it was not surprising to us that we encountered some degree of difficulty in achieving this coupling. Activation of the C-1 hydroxyl group using *O*-mesylation and iodination/bromination[31] was carried out, but the attempted coupling of these to the base or the silylated-base proved unsuccessful. Interestingly, when we attempted to couple the 1-*O*-mesylated-6-thio-β-D-sugar **35** with the silyl-activated base, we obtained the dimeric-6-*S*-linked sugar **36** under various conditions (Scheme 4).



Scheme 4. Reagents and conditions: (a) **35** (1 equiv), uracil (4 equiv), HMDS, TMSCl (0.1 equiv), DMF, 125 °C, 5 h.

Our previous work[21] enabled us to readily facilitate the hydrazine acetate mediated coupling between the C-6 thiolacetate derivatives **7α** (uracil), **14α** (5-fluorouracil) and **15α** (cytosine) and the methyl, ethyl and phenyl 2-bromopropionate moieties (excluding R = methyl, base = cytosine) to afford the sialyl mimetics **16**–**23** as mixtures of diastereomers in respectable yield. Treatment of the sialyl mimetics **16**–**23** with dilute NaOH (1.0 M) provided the de-esterified sialyl mimetics in good yield following purification by HPLC.

3. Conclusions

We have developed a route for the preparation of sialylnucleoside mimetics based on the common inexpensive carbohydrate D-fructose that will provide an interesting series of chemical probes for biological investigations of sialylnucleotide recognizing proteins.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Brüker Avance 300 MHz spectrometer. Chemical shifts are given in ppm relative to the solvent used ($CDCl_3$: 7.26 for ^{1}H, 77.0 for ^{13}C; D_2O: 4.70 for ^{1}H; MeOD: 3.30 for ^{1}H, 49.0 for ^{13}C). Assignments indicated with an asterisk (*) correspond to resonances clearly due to the corresponding diastereomer where such mixtures exist. Assignments indicated with a (†) denote assignments, which are interchangeable. Two-dimensional COSY and HSQC experiments were recorded to assist with spectral assignment. Low-resolution ESI mass spectra

were obtained using a Brüker Daltonics Esquire 3000 Ion Trap LC mass spectrometer, using ESI in the positive mode. High-resolution mass spectrometry was performed at the Department of Chemistry, University of Queensland, Australia, using a Finnigan MAT 900 XL Trap with a Finnigan AP1 III sprayer. Elemental analyses were performed by the microanalysis service at the Department of Chemistry, University of Queensland, Australia and were recorded on a Carlo Erba Elemental Microanalyser, model 1106. High pressure liquid chromatography (HPLC) was performed on an Agilent 1100 series system. All solvents were distilled prior to use or were of HPLC grade.

4.1. Methyl α/β-D-fructofuranosides 12α and 12β and methyl β-D-fructopyranoside 11

To a solution of D-fructose (20.0 g, 0.111 mol) in dry MeOH (1000 mL) was added acetyl chloride (1 mL) at rt, N_2, and stirred for 16 h. It was neutralized with Amberlite IRA-400 (OH^-) resin, filtered, washed with MeOH and concentrated. The crude material was purified by anion exchange chromatography (Dowex 1 × 8-200, ^-OH form; distilled H_2O as the mobile phase), which yielded three products: **12α** (7.56 g, 38%, R_f 0.60 [6:4:1, EtOAc–*i*-PrOH–H_2O]), **12β** (6.68 g, 34%, R_f 0.45) and **11** (4.02 g, 20%, R_f 0.32) and a mixture of **12β** and **11** (1.48 g, 8%) all as clear amorphous masses, giving a total yield of 92%.[24] Small samples of compounds **12α** and **β** and **11** were acetylated for characterization purposes. The methyl fructosides (~100 mg) were dissolved in pyridine (2 mL) before adding acetic anhydride (1 mL) at rt, under N_2 and stirring for 20 h. Diluted with EtOAc (15 mL), washed with HCl (0.1 M, 10 mL), H_2O (2 × 15 mL), dried over Na_2SO_4 and concentrated. Compound **12α** per-acetylated: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04, 2.08, 2.09, 2.10 (12H, 4 × s, 4 × OAc), 3.31 (3H, s, OMe), 4.11 (1H, d, $J_{1,1'}$ = 12.3 Hz, H-1), 4.12 (2H, m, H-5, H-6), 4.42 (1H, d, $J_{1',1}$ = 12.3 Hz, H-1′), 4.44 (1H, dd, $J_{6',5}$ = 3.0, $J_{6',6}$ = 11.4 Hz, H-6′), 4.93 (1H, dd, $J_{4,3}$ = 1.8, $J_{4,5}$ = 5.1 Hz, H-4), 5.30 (1H, d, $J_{3,4}$ = 1.8 Hz, H-3). Compound **12β** per-acetylated: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08, 2.09, 2.10, 2.12 (12H, 4 × s, 4 × OAc), 3.37 (3H, s, OMe), 4.17 (1H, d, $J_{1,1'}$ = 12.0 Hz, H-1), 4.17–4.23 (2H, m, H-5, H-6), 4.26 (1H, d, $J_{1',1}$ = 12.0 Hz, H-1′), 4.35 (1H, dd, $J_{6',5}$ = 6.6, $J_{6',6}$ = 14.1 Hz, H-6′), 5.41 (1H, dd, $J_{4,5}$ = 5.7, $J_{4,3}$ = 7.2 Hz, H-4), 5.49 (1H, d, $J_{3,4}$ = 7.2 Hz, H-3). Compound **11** per-acetylated: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98, 2.08, 2.11, 2.17 (12H, 4 × s, 4 × OAc), 3.35 (3H, s, OMe), 3.81 (1H, dd, $J_{6,5}$ = 1.5, $J_{6,6'}$ = 13.2 Hz, H-6), 3.87 (1H, dd, $J_{6',5}$ = 1.5, $J_{6',6}$ = 13.2 Hz, H-6′), 4.09 (1H, d, $J_{1,1'}$ = 12.0 Hz, H-1), 4.31 (1H, d, $J_{1',1}$ = 12.0 Hz, H-1′), 5.32–5.37 (2H, m, H-3, H-5), 5.53 (1H, dd, $J_{4,5}$ = 1.8, $J_{4,3}$ = 11.7 Hz, H-4).

4.2. Methyl 3,4-anhydro-α-D-tagatofuranoside 13α

To a solution of **1** (1.93 g, 9.92 mmol; dried over P_2O_5 overnight) in *N*,*N*-DMF (30 mL) was added triphenylphosphine (PPh_3; 6.63 g, 25.3 mmol, 2.5 equiv) at rt, under N_2 at 0 °C. Diisopropyl azodicarboxylate (DIAD; 5.0 mL, 25.4 mmol, 2.6 equiv) was added dropwise with stirring. The mixture was warmed to rt, stirred for 40 h and concentrated under reduced pressure. Crude material was taken up in H_2O (300 mL), washed with EtOAc (3 × 75 mL) and concentrated. This material was purified by flash column chromatography (20:1 → 3:2, $CHCl_3$–acetone) to afford **13α** as a pale yellow amorphous mass (1.22 g, 70%).[24] A small portion of material was per-acetylated (see the above procedure) for characterization purposes. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05, 2.07 (6H, 2 × s, 2 × OAc), 3.27 (3H, s, OMe), 3.66 (1H, d, $J_{3,4}$ = 2.7 Hz, H-3†), 3.74 (1H, d, $J_{4,3}$ = 2.7 Hz, H-4†), 3.91 (1H, d, $J_{1,1'}$ = 12.0 Hz, H-1), 4.19 (3H, s, H-5, H-6, H-6′), 4.44 (1H, d, $J_{1',1}$ = 12.0 Hz, H-1′).

4.3. Methyl 3,4-anhydro-β-D-tagatofuranoside 13β

The following was prepared in a similar manner to **13α**. Reaction of **12β** (3.76 g, 19.35 mmol) yielded **13β** (3.01 g, 88%) as a clear amorphous mass.[24] A small portion of material was per-acetylated (see procedure above) for characterization purposes. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (6H, s, 2 × OAc), 3.46 (3H, s, OMe), 3.65 (1H, d, $J_{3,4}$ = 2.7 Hz, H-3†), 3.68 (1H, d, $J_{4,3}$ = 2.7 Hz, H-4†), 4.01 (1H, d, $J_{1,1'}$ = 12.0 Hz, H-1), 4.14 (1H, d, $J_{5,6/6'}$ = 5.7 Hz, H-5), 4.21(1H, d, $J_{1',1}$ = 12.0 Hz, H-1′), 4.26 (2H, d, $J_{6/6',5}$ = 5.7 Hz, H-6/6′).

4.4. Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-α-D-tagatofuranoside 8α and

4.5. Methyl 1,6-di-*S*-acetyl-3,4-anhydro-1,6-di-thio-α-D-tagatofuranoside 34α

To a solution of **13α** (0.91 g, 5.16 mmol) in dry THF (20 mL) and 4 Å molecular sieves, were added PPh_3 (1.60 g, 6.10 mmol, 1.2 equiv) and DIAD (1.20 mL, 6.10 mmol, 1.2 equiv) at −10 °C, under N_2, stirred for 15 min and then warmed to 0 °C for solubility purposes. Thiolacetic acid (370 μL, 5.18 mmol, 1.0 equiv) was added and the mixture warmed to 4 °C and stirred for 20 h, at which time an additional 0.2 equiv of thiolacetic acid was added (80 μL, 1.04 mmol) and stirred for a further 4 h. The reaction mixture was filtered, washed with EtOAc and concentrated. The organic phase extracted into EtOAc (300 mL) and washed with HCl (0.1 M, 100 mL), H_2O (100 mL), satd aq $NaHCO_3$ (100 mL), dried (Na_2SO_4) and concentrated. Upon TLC of aqueous washes, the presence of the desired material was identified, and the aqueous phases combined, washed with EtOAc (2 × 100 mL), dried over Na_2SO_4 and the organic phase added to the original organic phase and concentrated. This material was purified by flash column chromatography ($CHCl_3$ → 10:1, $CHCl_3$–acetone) to yield **8α** (1.14 g, 94%) as a pale yellow amorphous mass and **34α** (25.1 mg, 2%) as a yellow oil. Compound **8α**: HRMS: $[M+Na]^+$ 315.0340; $C_{11}H_{16}O_5S_2$ + Na requires 315.0337. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (3H, s, SAc), 3.10 (1H, dd, $J_{6,5}$ = 6.9, $J_{6,6'}$ = 13.8 Hz,

H-6), 3.16 (1H, dd, $J_{6',5}$ = 6.6, $J_{6',6}$ = 13.8 Hz, H-6′), 3.34 (3H, s, OMe), 3.65 (1H, d, $J_{1,1'}$ = 11.7 Hz, H-1), 3.73 (1H, d, $J_{3,4}$ = 3.0 Hz, H-3†), 3.76 (1H, d, $J_{4,3}$ = 3.0 Hz, H-4†), 3.81 (1H, d, $J_{1',1}$ = 11.7 Hz, H-1′), 4.14 (1H, dd, $J_{5,6'}$ = 6.6, $J_{5,6}$ = 6.9 Hz, H-5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.8 (C-6), 30.5 (SC(O)*C*H$_3$), 49.5 (OCH_3), 56.0 (C-3†), 57.6 (C-4†), 60.0 (C-1), 76.4 (C-5), 105.3 (C-2), 195.0 (S*C*(O)CH$_3$). **34α**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36, 2.37 (6H, 2 × s, 2 × SAc), 3.14 (2H, dd, $J_{6/6',4}$ = 1.2, $J_{6/6',5}$ = 6.6 Hz, H-6/6′), 3.27 (3H, s, OMe), 3.28 (1H, d, $J_{1,1'}$ = 14.4 Hz, H-1), 3.42 (1H, d, $J_{1',1}$ = 14.4 Hz, H-1′), 3.59 (1H, d, $J_{3,4}$ = 2.7 Hz, H-3†), 3.71 (1H, d, $J_{4,3}$ = 2.7 Hz, H-4†), 4.09 (1H, dd, $J_{5,6}$ = $J_{5,6'}$ = 6.6 Hz, H-5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.8 (C-6), 29.5 (C-1), 30.4, 30.5 (2 × SC(O)*C*H$_3$), 49.5 (OCH_3), 56.1 (C-3†), 58.3 (C-4†), 76.7 (C-5), 105.1 (C-2), 194.2, 195.0 (2 × S*C*(O)CH$_3$).

4.6. Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-β-D-tagatofuranoside 8β and

4.7. Methyl 1,6-di-*S*-acetyl-3,4-anhydro-1,6-di-thio-β-D-tagatofuranoside 34β

To a solution of **13β** (3.71 g, 21.1 mmol) in dry THF (60 mL) and 4 Å molecular sieves, were added PPh_3 (6.64 g, 25.3 mmol, 1.2 equiv) and DIAD (5.0 mL, 25.4 mmol, 1.2 equiv) at −10 °C, under N_2 and stirred for 15 min, after which it was allowed to warm to 0 °C. Thiolacetic acid (1.5 mL, 21.0 mmol, 1.0 equiv) was added and the mixture stirred at 4 °C for 18 h. The reaction mixture was filtered, washed with EtOAc and concentrated. The organic phase extracted into EtOAc (300 mL) and washed with HCl (0.1 M, 75 mL), H_2O (75 mL), satd aq $NaHCO_3$ (75 mL), dried over Na_2SO_4 and concentrated. The aqueous phases were combined, washed with EtOAc (2 × 100 mL) and organic phase dried over Na_2SO_4, added to the original organic phase and concentrated. Ph_3PO was partially removed by recrystallization from EtOAc and hexane. The mother liquor was purified initially by passing through a plug of silica ($CHCl_3$), then flash column chromatography (3:1, hexane–EtOAc → 3:2, EtOAc–hexane) to yield **8β** (3.71 g, 75%) as a pale yellow powder and **34β** (1.33 g, 22%) as a yellow amorphous mass. Compound **8β**: HRMS: $[M+Na]^+$ 315.0341; $C_{11}H_{16}O_5S_2$ + Na requires 315.0337. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (3H, s, SAc), 3.20 (2H, d, $J_{6/6',5}$ = 6.6 Hz, H-6/6′), 3.52 (3H, s, OCH_3), 3.53 (1H, d, $J_{1,1'}$ = 11.7 Hz, H-1), 3.64 (1H, d, $J_{1',1}$ = 11.7 Hz, H-1′), 3.68 (1H, dd, $J_{4,5}$ = 0.9, $J_{4,3}$ = 3.0 Hz, H-4), 3.73 (1H, d, $J_{3,4}$ = 3.0 Hz, H-3), 3.99 (1H, ddd, $J_{5,4}$ = 0.9, $J_{5,6}$ = $J_{5,6'}$ = 6.6 Hz, H-5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.8 (C-6), 30.5 (SC(O)*C*H$_3$), 52.6 (OCH_3), 54.7 (C-4), 57.0 (C-3), 65.1 (C-1), 75.2 (C-5), 104.9 (C-2), 195.1 (S*C*(O)CH$_3$). **34β**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36, 2.37 (6H, 2 × s, 2 × SAc) 3.14 (1H, d, $J_{1,1'}$ = 14.1 Hz, H-1), 3.19 (2H, d, $J_{6/6',5}$ = 6.9 Hz, H-6/6′), 3.20 (1H, d, $J_{1',1}$ = 14.1 Hz, H-1′), 3.47 (3H, s, OMe), 3.58 (1H, d, $J_{3,4}$ = 3.0 Hz, H-3), 3.68 (1H, dd, $J_{4,5}$ = 0.9, $J_{4,3}$ = 3.0 Hz, H-4), 4.03 (1H, ddd, $J_{5,4}$ = 0.9, $J_{5,6}$ = $J_{5,6'}$ = 6.9 Hz, H-5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.6 (C-6), 30.4, 30.5 (2 × SC(O)*C*H$_3$), 33.9 (C-1), 52.7 (OCH_3), 54.5 (C-4), 57.1 (C-3), 74.8 (C-5), 104.7 (C-2), 194.8, 194.9 (2 × S*C*(O)CH$_3$).

4.8. Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-1-*O*-trifluoromethanesulfonate-α-D-tagatofuranoside 9

A solution of **8α** (1.00 g, 4.27 mmol) in dry CH_2Cl_2 (20 mL) under Ar was cooled to −78 °C before the addition of pyridine (1.10 mL, 13.7 mmol, 3.2 equiv), then trifluoromethanesulfonic anhydride (Tf_2O; 1.08 mL, 6.40 mmol, 1.5 equiv) dropwise. This mixture was stirred for 10 min, warmed to 0 °C, stirred for 1 h and concentrated. The crude material was taken up in CH_2Cl_2 (10 mL) and washed with HCl (1 M, 20 mL), H_2O (2 × 20 mL), dried over Na_2SO_4 and concentrated. It was purified by flash column chromatography (4:1, hexane–EtOAc) to furnish **9** (1.24 g, 79%) as a pale yellow viscous oil. HRMS: $[M+Na]^+$ 388.9953; $C_{10}H_{13}F_3O_7S_2$ + Na requires 388.9952. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (3H, s, SAc), 3.09 (1H, dd, $J_{6,5}$ = 6.9, $J_{6,6'}$ = 13.8 Hz, H-6), 3.14 (1H, dd, $J_{6',5}$ = 6.3, $J_{6',6}$ = 13.8 Hz, H-6′), 3.36 (3H, s, OMe), 3.76 (1H, d, $J_{3,4}$ = 3.0 Hz, H-3†), 3.83 (1H, d, $J_{4,3}$ = 3.0 Hz, H-4†), 4.19 (1H, dd, $J_{5,6'}$ = 6.3, $J_{5,6}$ = 6.9 Hz, H-5), 4.38 (1H, d, $J_{1,1'}$ = 10.8 Hz, H-1), 4.61 (1H, d, $J_{1',1}$ = 10.8 Hz, H-1′). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.6 (C-6), 30.5 (SC(O)*C*H$_3$), 49.7 (OCH_3), 56.7 (C-4†), 57.4 (C-3†), 69.9 (C-1), 77.2 (C-5), 102.8 (C-2), 112.2, 116.4, 120.6, 124.9 (CF_3), 194.8 (S*C*(O)CH$_3$).

4.9. 1-(Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-α-D-tagatofuranoside)-uracil 7α

Method A: To a suspension of uracil (3.8 g, 33.8 mmol, 10 equiv), dried over P_2O_5, in hexamethyl disilazane (HMDS; 30 mL), was added TMSCl (43 μL, 0.338 mmol, 0.1 equiv) at rt, under N_2. The mixture was heated to reflux and stirred for 16 h before concentrating under reduced pressure and opening to an atmosphere of Ar. A solution of **9** (1.24 g, 3.38 mmol) in 1,2-dichloroethane (30 mL) was added to the silylated uracil at 0 °C, under Ar and stirred for 10 min and then warmed to 60 °C for 2 days. The reaction mixture was filtered through Celite, washed with CH_2Cl_2 and concentrated. The crude material was absorbed onto non-flash silica and purified by flash column chromatography (3:2, EtOAc, hexane) affording the desired material **7α** as a white foam (1.10 g, 99%), which was then recrystallized from EtOAc/hexane to yield the white crystalline product (0.70 g, 63%). HRMS: $[M+Na]^+$ 351.0625; $C_{13}H_{16}N_2O_6S$ + Na requires 351.0627. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (3H, s, SAc), 3.01 (1H, dd, $J_{6'a,5}$ = 6.9, $J_{6'a,6'b}$ = 13.8 Hz, H-6′a), 3.12 (1H, dd, $J_{6'b,5}$ = 6.9, $J_{6'b,6'a}$ = 13.8 Hz, H-6′b), 3.36 (3H, s, OMe), 3.65 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.68 (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′†), 3.73 (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′†), 4.16 (1H, dd, $J_{5',6'a}$ = $J_{5',6'b}$ = 6.9 Hz, H-5′), 4.43 (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 5.66 (1H, dd, $J_{5,3}$ = 1.5, $J_{5,6}$ = 8.1 Hz, H-5), 7.20 (1H, d, $J_{6,5}$ = 8.1 Hz, H-6), 8.62 (1H, br s, NH-3). ^{13}C

NMR (75.5 MHz, $CDCl_3$): δ 28.7 (C-6′), 30.5 (SC(O)*C*H$_3$), 48.2 (C-1′), 50.2 (OCH$_3$), 55.8 (C-4′†), 58.2 (C-3′†), 77.2 (C-5′), 101.5 (C-5), 103.6 (C-2′), 145.3 (C-6), 151.0 (C-2), 163.5 (C-4), 194.9 (S*C*(O)CH$_3$).

Method B: Uracil (245 mg, 2.18 mmol, 4 equiv), dried over P_2O_5, was suspended in HMDS (10 mL), to which TMSCl (7.0 μL, 0.0546 mmol, 0.1 equiv) was added at rt, under N_2. The mixture was heated to reflux and stirred for 16 h before concentrating under reduced pressure and opening to an atmosphere of Ar. To a solution of **9** (200 mg, 0.546 mmol) in 1,2-DCE at 0 °C, under Ar, was added the silylated uracil and Et_3N (67 μL; 0.546 mmol, 1 equiv) with stirring for 10 min before heating to 50 °C for 6 days. The reaction mixture was filtered through Celite (washed with CH_2Cl_2), concentrated and purified by flash column chromatography (3:2, EtOAc–hexane) to yield **7α** (122 mg, 68%) as a white foam.

4.10. 1-(Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-α-D-tagatofuranoside)-5-fluorouracil 14α

The following compound was prepared in a similar manner to Method A from Section 4.9. Product **14α** was obtained in 54% yield as a fine white powder. HRMS: $[M+Na]^+$ 369.0534; $C_{13}H_{15}FN_2O_6S$ + Na requires 369.0533. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (3H, s, SAc), 3.00 (1H, dd, $J_{6'a,5'}$ = 6.6, $J_{6'a,6'b}$ = 13.8 Hz, H-6′a), 3.12 (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.8 Hz, H-6′b), 3.35 (3H, s, OMe), 3.62 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.71 (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.73 (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.17 (1H, dd, $J_{5',6'a} = J_{5',6'b}$ = 6.6 Hz, H-5′), 4.41 (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 7.32 (1H, d, $J_{6,F}$ = 5.7 Hz, H-5). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.7 (C-6′), 30.5 (SC(O)*C*H$_3$), 48.6 (C-1′), 50.3 (OCH$_3$), 55.7 (C-4′)†, 58.0 (C-3′)†, 77.1 (C-5′), 103.5 (C-2′), 129.6 (d, $J_{6,F}$ = 33.8 Hz, C-6), 140.0 (d, $J_{5,F}$ = 241 Hz, C-5), 150.2 (C-2), 157.5 (d, $J_{4,F}$ = 26.2 Hz, C-4), 194.9 (S*C*(O)CH$_3$).

4.11. 1-(Methyl 6-*S*-acetyl-3,4-anhydro-6-thio-α-D-tagatofuranoside)-cytosine 15α

The following compound was prepared in a similar manner to Method A from Section 4.9. The desired material **15α** was furnished as a fine white powder in 79% yield. HRMS: $[M+Na]^+$ 350.0793; $C_{13}H_{17}N_3O_5S$ + Na requires 350.0787. ^{1}H NMR (300 MHz, MeOD): δ 2.35 (3H, s, SAc), 3.02 (1H, dd, $J_{6'a,5'}$ = 6.6, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 3.10 (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.36 (3H, s, OMe), 3.68 (1H, d, $J_{3',4'}$ = 3.0 Hz, H-3′)†, 3.76 (1H, d, $J_{4',3'}$ = 3.0 Hz, H-4′)†, 3.86 (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 4.12 (1H, dd, $J_{5',6'a} = J_{5',6'b}$ = 6.6 Hz, H-5′), 4.40 (1H, d, $J_{1'b,1'a}$ = 14.1 Hz, H-1′b), 5.82 (1H, d, $J_{5,6}$ = 7.2 Hz, H-5), 7.46 (1H, d, $J_{6,5}$ = 7.2 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 29.6 (C-6′), 30.4 (SC(O)*C*H$_3$), 50.3 (C-1′), 50.5 (OCH$_3$), 56.6 (C-4′)†, 59.5 (C-3′)†, 78.3 (C-5′), 95.3 (C-5), 105.2 (C-2′), 148.5 (C-6), 159.2 (C-2), 167.8 (C-4), 196.4 (S*C*(O)CH$_3$).

4.12. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(ethyl propionate)]-α-D-tagatofuranoside)-uracil 16

A solution of **7α** (200 mg, 0.609 mmol) in *N,N*-DMF (5 mL) was degassed with N_2 for 5 min before the addition of 4 Å molecular sieves. Hydrazine acetate (84 mg, 0.914 mmol, 1.5 equiv) was added at rt, under N_2 and stirred for 30 min, after which Et_3N (93 μL, 0.670 mmol, 1.1 equiv) and ethyl 2-bromopropionate (87 μL, 0.670 mmol, 1.1 equiv) were added under the same conditions and stirring continued for a further 3 h. The reaction mixture was filtered through Celite, washed with EtOAc and concentrated and purified by flash column chromatography (neat EtOAc) to yield **16** as a clear, pale yellow oil (140 mg, 60%). HRMS: $[M+Na]^+$ 409.1041; $C_{16}H_{22}N_2O_7S$ + Na requires 409.1045. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29, 1.30* (3H, t, J = 7.2 Hz, COOCH$_2$*C*H$_3$), 1.46 (3H, d, $J_{3'',2''}$ = 6.9 Hz, H-3″), 2.71, 2.79* (1H, dd, $J_{6'a,5'}$ = 7.5, $J_{6'a,6'b}$ = 13.2 Hz, H-6′a), 2.85, 2.91* (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.2 Hz, H-6′b), 3.36, 3.37* (3H, s, OMe), 3.43, 3.46* (1H, q, $J_{2'',3''}$ = 6.9 Hz, H-2″), 3,64, 3.65* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.68. 3.69* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.79, 3.81* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.20 (2H, q, J = 7.2 Hz, COO*C*H$_2$CH$_3$), 4.22 (1H, dd, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.5 Hz, H-5′), 4.42, 4.43* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H1′b), 5.65, 5.66* (1H, dd, $J_{5,3}$ = 2.1, $J_{5,6}$ = 7.8 Hz, H-5), 7.22, 7.23* (1H, d, $J_{6,5}$ = 7.8 Hz, H-6), 8.33 (1H, br s, NH-3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1 (COOCH$_2$*C*H$_3$), 17.2, 17.3* (C-3″), 30.5, 31.0* (C-6′), 41.4, 41.9* (C-2″), 48.1 (C-1′), 50.1 (OCH$_3$), 55.7, 55.8* (C-4′), 58.1, 58.2* (C-3′), 61.3 (COO*C*H$_2$CH$_3$), 77.7, 78.0* (C-5′), 101.4, 101.5* (C-5), 103.5, 103.6* (C-2′), 145.3 (C-6), 151.3 (C-2), 163.8 (C-4), 172.4, 172.8* (C-1″).

4.13. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl butyrate)]-α-D-tagatofuranoside)-uracil 17

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **17** was prepared in 92% yield by coupling between **7α** and methyl 2-bromobutyrate (chromatography neat EtOAc) as a clear oil. HRMS: $[M+Na]^+$ 409.1043; $C_{16}H_{22}N_2O_7S$ + Na requires 409.1045. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, $J_{4'',3''}$ = 7.2 Hz, H-4″), 1.80 (2H, ddq, H-3″), 2.68, 2.75* (1H, dd, $J_{6'a,5'}$ = 7.8, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.81, 2.86* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.21, 3.25* (1H, dd, $J_{2'',3''a}$ = 7.2, $J_{2'',3''b}$ = 8.1 Hz, H-2″), 3.36, 3.37* (3H, s, OMe), 3.62, 3.64* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.68, 3.69* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′), 3.74, 3.75* (3H, s, COOMe), 3.77, 3.80* (1H, dd, $J_{4',5'}$ = 0.6, $J_{4',3'}$ = 2.7 Hz, H-4′), 4.19 (1H, ddd, $J_{5',4'}$ = 0.6, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 7.8 Hz, H-5′), 4.43, 4.44* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 5.64, 5.65* (1H, dd, $J_{5,3}$ = 2.4, $J_{5,6}$ = 8.1 Hz, H-5), 7.22, 7.23 (1H, d, $J_{6,5}$ = 8.1 Hz, H-6), 8.80 (1H, br s, NH-3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9 (C-4″) 24.8, 25.0* (C-3″), 30.5, 30.9* (C-6′), 48.2 (C-1′), 48.6, 49.0* (C-2″), 50.2 (OCH$_3$), 52.3 (COO*C*H$_3$), 55.7, 55.8* (C-4′), 58.1, 58.2* (C-3′), 77.8, 78.0* (C-5′), 101.4, 101.5* (C-5), 103.4, 103.6* (C-2′), 145.3 (C-6), 151.3 (C-2), 163.9 (C-4), 172.9, 173.0* (C-1″).

4.14. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl-2-phenylacetate)]-α-D-tagatofuranoside)-uracil 18

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **18** was prepared in 59% yield by coupling between **7α** and methyl α-bromophenylacetate (chromatography 2:1, EtOAc–hexane) as a clear oil. HRMS: $[M+Na]^+$ 457.1040; $C_{20}H_{22}N_2O_7S$ + Na requires 457.1045. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55, 2.65* (1H, dd, $J_{6'a,5'}$ = 7.2/7.8*, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.73, 2.74* (1H, dd, $J_{6'b,5'}$ = 6.3/6.6*, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.32, 3.33* (3H, s, OMe), 3.59 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.65, 3.68* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.70, 3.77* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 3.73, 3.74* (3H, s, COOMe), 4.09 (1H, dd, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.2 Hz, H-5′), 4.41 (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.63, 4.64* (1H, s, H-2″), 5.56, 5.60* (1H, dd, $J_{5,3}$ = 2.1, $J_{5,6}$ = 7.8 Hz, H-5), 7.14, 7.16* (1H, d, $J_{6,5}$ = 7.8 Hz, H-6), 7.31–7.41 (5H, m, Ph), 8.82, 8.84* (1H, s, NH-3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.8, 31.3* (C-6′), 48.2 (C-1′), 50.1 (OCH_3), 52.6, 52.7* ($COOCH_3$), 52.9 (C-2″), 55.6 (C-4)†, 58.3 (C-3)†, 77.8 (C-5′), 101.5 (C-5), 103.4 (C-2′), 128.3, 128.4, 128.5, 128.9 (Ph), 145.2 (C-6), 151.2 (C-2), 163.5 (C-4), 170.9 (C-1″).

4.15. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(ethyl propionate)]-α-D-tagatofuranoside)-5-fluorouracil 19

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **19** was prepared in 84% yield by coupling between **14α** and ethyl 2-bromopropionate (chromatography 3:2, EtOAc–hexane) as a clear amorphous mass. HRMS: $[M+Na]^+$ 427.0947; $C_{16}H_{21}FN_2O_7S$ + Na requires 427.0951. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, J = 7.2 Hz, $COOCH_2CH_3$), 1.46 (3H, d, $J_{3'',2''}$ = 7.2 Hz, H-3″), 2.73, 2.80* (1H, dd, $J_{6'a,5'}$ = 7.5, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.86, 2.93* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.36, 3.37* (3H, s, OMe), 3.42, 3.46* (1H, q, $J_{2'',3''}$ = 7.2 Hz, H-2″), 3.60, 3.62* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.70, 3.71* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.80, 3.82* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.20 (2H, q, J = 7.2 Hz, $COOCH_2CH_3$), 4.24 (1H, dd, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 7.5 Hz, H-5′), 4.41, 4.42* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 7.35, 7.36* (1H, d, $J_{6,F}$ = 6.0 Hz, H-6). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1 (C-3″), 17.1, 17.2* ($COOCH_2CH_3$), 30.6, 30.9* (C-6′), 41.4, 41.9* (C-2″), 48.5 (C-1′), 50.2 (OCH_3), 55.7 (C-4′)†, 58.0, 58.1* (C-3′)†, 61.3 ($COOCH_2CH_3$), 77.7, 77.9* (C-5′), 103.3, 103.4* (C-2′), 129.6 ($J_{6,F}$ = 33.2 Hz, C-6), 139.9 ($J_{5,F}$ = 235.6 Hz, C-5), 150.2 (C-2), 157.4 ($J_{4,F}$ = 26.4 Hz, C-4), 172.7, 172.8* (C-1″).

4.16. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl butyrate)]-α-D-tagatofuranoside)-5-fluorouracil 20

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **20** was prepared in 87% yield by coupling between **14α** and methyl 2-bromobutyrate (chromatography 3:2, EtOAc–hexane) as a clear amorphous mass. HRMS: $[M+Na]^+$ 427.0948; $C_{16}H_{21}FN_2O_7S$ + Na requires 427.0951. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, H-4″), 1.81 (2H, dq, H-3″), 2.69, 2.75* (1H, dd, $J_{6'a,5'}$ = 7.2, $J_{6'a,6'b}$ = 13.2 Hz, H-6′a), 2.82, 2.87* (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.2 Hz, H-6′b), 3.20, 3.25* (1H, t, H-2″), 3.36, 3.37* (3H, s, OMe), 3.59, 3.61* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.71, 3.72* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.75 (3H, s, COOMe), 3.78, 3.80* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.21, 4.22* (1H, dd, $J_{5'6'b}$ = 6.6, $J_{5'6'a}$ = 7.2 Hz, H-5′), 4.42, 4.44* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 7.35, 7.36* (1H, d, $J_{6,F}$ = 6.0 Hz, H-6), 9.38 (NH-3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9 (C-4″), 24.3, 25.0* (C-3″), 30.6, 30.9* (C-6′), 48.5 (C-1′), 48.6, 49.1* (C-2″), 50.2 (OCH_3), 52.3 ($COOCH_3$), 55.7 (C-4′)†, 58.0, 58.1* (C-3′)†, 77.9, 78.0 (C-5′), 103.3, 103.4 (C-2′), 129.6 ($J_{6,F}$ = 33.2 Hz, C-6), 139.9 ($J_{5,F}$ = 234.8 Hz, C-5), 150.1 (C-2), 157.3 ($J_{4,F}$ = 25.7 Hz, C-4), 172.9, 173.0* (C-1″).

4.17. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl-2-phenylacetate)]-α-D-tagatofuranoside)-5-fluorouracil 21

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **21** was prepared in 90% yield by coupling between **14α** and methyl α-bromophenylacetate (chromatography 3:1, EtOAc–hexane) as a white foam. HRMS: $[M+Na]^+$ 475.0946; $C_{20}H_{21}FN_2O_7S$ + Na requires 475.0951. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58, 2.66* (1H, dd, $J_{6'a,5'}$ = 7.5, $J_{6'a,6'b}$ = 13.2 Hz, H-6′a), 2.76, 2.77* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.2 Hz, H-6′b), 3.32, 3.33* (3H, s, OMe), 3.57 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.66, 3.68* (1H, d, $J_{3',4'}$ = 3.0 Hz, H-3′)†, 3.73, 3.78* (1H, d, $J_{4',3'}$ = 3.0 Hz, H-4′)†, 3.75 (3H, s, COOMe), 4.10, 4.12* (1H, dd, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 7.5 Hz, H-5′), 4.39 (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.62, 4.65* (1H, s, H-2″), 7.28, 7.31* (1H, d, $J_{6,F}$ = 6.0 Hz, H-6), 7.29–7.46 (5H, m, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 30.9, 31.4* (C-6′), 48.6 (C-1′), 50.2, 50.3* (OCH_3), 52.7, 52.9* ($COOCH_3$), 55.6, 55.7* (C-4′)†, 58.0, 58.1* (C-3′)†, 77.8 (C-5′), 103.3, 103.4* (C-2′), 128.3, 128.4, 128.5, 128.6, 128.9 (Ph), 129.5, 129.6* ($J_{6,F}$ = 33.2 Hz, C-6), 135.5, 135.6* (*ipso*-Ph), 139.9 ($J_{5,F}$ = 236.3 Hz, C-5), 150.0 (C-2), 157.2 ($J_{4,F}$ = 26.4 Hz, C-4), 170.9, 171.1 (C-1″).

4.18. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl butyrate)]-α-D-tagatofuranoside)-cytosine 22

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **22** was prepared in 92% yield by coupling between **15α** and methyl 2-bromobutyrate (chromatography 5:1, EtOAc–MeOH) as a white foam. HRMS: $[M+Na]^+$ 408.1209; $C_{16}H_{23}N_3O_6S$ + Na requires 408.1205. ^{1}H NMR (300 MHz, MeOD): δ 1.01 (3H, t, $J_{4'',3''}$ = 7.2 Hz, H-4″), 1.65–1.93 (2H, m, H-3″), 2.68, 2.74* (1H, dd, $J_{6'a,5'}$ = 7.2, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.80, 2.84* (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.32–3.41 (1H, m, H-2″), 3.38, 3.39* (3H, s, OMe), 3.69, 3.70* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.73, 3.74* (3H, s, COOMe), 3.82 (1H, dd, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 3.85, 3.87* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 4.20, 4.22* (1H,

dd, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.2 Hz, H-5′), 4.41, 4.42* (1H, d, $J_{1'b,1'a}$ = 14.1 Hz, H-1′b), 5.84, 5.85* (1H, d, $J_{5,6}$ = 7.2 Hz, H-5), 7.49, 7.50* (1H, d, $J_{6,5}$ = 7.2 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 12.2, 12.3* (C-4″), 26.1, 26.3* (C-3″), 31.9, 32.3* (C-6′), 49.6, 50.2* (C-2″), 50.5 (C-1′), 50.7 (OCH_3), 52.9 ($COOCH_3$), 56.9 (C-4′), 59.7, 59.8* (C-3′), 79.3, 79.6* (C-5′), 95.4, 95.5* (C-5), 105.2, 105.3* (C-2′), 148.6, 148.7* (C-6), 159.4 (C-2), 167.8 (C-4), 175.0, 175.1* (C-1″).

4.19. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(methyl-2-phenylacetate)]-α-D-tagatofuranoside)-cytosine 23

The title compound was prepared in a similar manner to that described in Section 4.12. Thus, **23** was prepared in 99% yield by coupling between **15α** and methyl α-bromophenylacetate (chromatography 9:1, EtOAc–MeOH) as a white foam. HRMS: $[M+H]^+$ 434.1382; $C_{20}H_{23}N_3O_6S$ + H requires 434.1386. ^{1}H NMR (300 MHz, MeOD): δ 2.55 (1H, dd, $J_{6'a,5'}$ = 7.2, $J_{6'a,6'b}$ = 13.8 Hz, H-6′a), 2.66* (2H, d, $J_{6'a/6'b*,5'}$ = 6.9 Hz, H-6′a*, H-6′b*), 2.73 (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.8 Hz, H-6′b), 3.33, 3.34* (3H, s, OMe), 3.67, 3.69* (1H, d, $J_{3',4'}$ = 3.0 Hz, H-3′), 3.71, 3.72* (3H, s, COOMe), 3.78, 3.80* (1H, dd, $J_{4',5'}$ = 0.6, $J_{4',3'}$ = 3.0 Hz, H-4′), 3.83, 3.84* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 4.11, 4.13* (1H, ddd, $J_{5',4'}$ = 0.6, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.2 Hz, H-5′), 4.39 (1H, d, $J_{1'b,1'a}$ = 14.1 Hz, H-1′b), 4.82, 4.83* (1H, s, H-2″), 5.79, 5.83* (1H, d, $J_{5,6}$ = 7.8 Hz, H-5), 7.31–7.48 (5H, m, Ph), 7.35 (1H, d, $J_{6,5}$ = 7.8 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 32.1, 32.5* (C-6′), 50.5 (C-1′), 50.6, 50.7* (OCH_3), 53.4 ($COOCH_3$), 53.6, 53.7* (C-2″), 56.8, 57.0* (C-4′), 59.8, 59.9* (C-3′), 79.3, 79.4* (C-5′), 95.4 (C-5), 105.1, 105.2* (C-2′), 129.5, 129.7, 129.8, 129.9, 130.0 (Ph), 137.8, 137.9* (*ipso*-Ph), 148.8 (C-6), 158.8 (C-2), 167.4 (C-4), 173.0, 173.1* (C-1″).

4.20. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium propionate)]-α-D-tagatofuranoside)-uracil 24

To a solution of **16** (107 mg, 0.277 mmol) in MeOH (5 mL) was added 1 M NaOH (1 mL) at rt, under N_2 and stirred for 16 h. It was neutralized by Amberlite IR-120 (H^+) resin (to ~pH 5), filtered, washed with aqueous MeOH and concentrated under reduced pressure. The crude material was dissolved in MeOH (5-10 mL) and the pH adjusted to 7.3–7.5 with 0.5–0.05 M NaOH to form the sodium salt, concentrated and then freeze-dried. The residue was purified by HPLC (Phenomenex Aqua C18 reverse phase column, 85:15 H_2O–CH_3CN, 2.5 mL/min) to give **24** (65.8 mg, 63%) as a white solid. Anal. Calcd for $C_{14}H_{17}N_2O_7SNa + 1.5H_2O$: C, 41.25; H, 4.95; N, 6.87. Found: C, 40.95; H, 4.81; N, 6.52. HRMS: $[M+H]^+$ 381.0728; $C_{14}H_{17}N_2O_7SNa$ + H requires 381.0732. ^{1}H NMR (300 MHz, MeOD): δ 1.36, 1.38* (3H, d, $J_{3'',2''}$ = 7.2 Hz, H-3″), 2.58, 2.66* (1H, dd, $J_{6'a,5'}$ = 7.8, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.77, 2.83* (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.36, 3.37* (3H, s, OMe), 3.39, 3.42* (1H, q, $J_{2'',3''}$ = 7.2 Hz, H-2″), 3.63, 3.64* (1H, d, $J_{3',4'}$ = 3.0 Hz, H-3′)†, 3.81 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.88, 3.89* (1H, d, $J_{4',3'}$ = 3.0 Hz, H-3′)†, 4.30, 4.31* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.31 (1H, dd, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.8 Hz, H-5′), 5.60, 5.61* (1H, d, $J_{5,6}$ = 7.8 Hz, H-5), 7.47, 7.48* (1H, d, $J_{6,5}$ = 7.8 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 19.1, 19.3* (C-3″), 31.5, 32.2* (C-6′), 46.6, 47.4* (C-2″), 49.3 (C-1′), 50.5 (OCH_3), 57.0, 57.1* (C-4′)†, 59.5 (C-3′)†, 79.3, 79.8* (C-5′), 101.4 (C-5), 104.8, 104.9* (C-2′), 148.3, 148.4* (C-6), 153.3 (C-2), 167.0 (C-4).

4.21. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium butyrate)]-α-D-tagatofuranoside)-uracil 25

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **17** gave in 62% yield **25** (HPLC: Phenomenex Aqua C18 reverse phase column, 70:30 H_2O–CH_3CN, 2.5 mL/min) as a white solid. Anal. Calcd for $C_{15}H_{19}N_2O_7SNa + 1.5H_2O$: C, 42.73; H, 5.26; N, 6.65. Found: 42.24; H, 5.10; N, 6.20. HRMS: $[M+H]^+$ 395.0888; $C_{15}H_{19}N_2O_7SNa$ + H requires 395.0889. ^{1}H NMR (300 MHz, MeOD): δ 0.95 (3H, t, $J_{4'',3''}$ = 7.2 Hz, H-4″), 1.64, 1.80* (2H, ddq, H-3″), 2.58, 2.66* (1H, dd, $J_{6'a,5'}$ = 8.1, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.76, 2.83* (1H, dd, $J_{6'b,5'}$ = 6.0, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.14, 3.19* (1H, dd, $J_{2'',3''a}$ = 7.2, $J_{2'',3''b}$ = 8.1 Hz, H-2″), 3.36, 3.37* (3H, s, OMe), 3.64 (1H, dd, $J_{4',3'}$ = $J_{4',5'}$ = 2.7 Hz, H-4′), 3.81 (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.88, 3.90* (1H, d, $J_{3',4'}$ = 2.7Hz, H-3′), 4.30, 4.32* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.33 (1H, ddd, $J_{5',4'}$ = 2.7, $J_{5',6'b}$ = 6.0, $J_{5',6'a}$ = 8.1 Hz, H-5′), 5.61 (1H, d, $J_{5,6}$ = 8.1 Hz, H-5), 7.47, 7.48* (1H, d, $J_{6.5}$ = 8.1 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 12.6, 12.7* (C-4″), 27.1, 27.3* (C-3″), 31.5, 32.3* (C-6′), 49.3 (C-1), 50.5 (OCH_3), 53.9, 54.7* (C-2″), 57.0, 57.1* (C-3′)†, 59.5 (C-4′)†, 79.3, 79.7* (C-5′), 101.4 (C-5), 104.8, 104.9* (C-2′), 148.3, 148.4* (C-6), 153.2 (C-2), 166.9 (C-4), 180.0 (C-1″).

4.22. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium-2-phenylacetate)]-α-D-tagatofuranoside)-uracil 26

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **18** gave **26** in 49% yield (HPLC: Phenomenex Aqua C18 reverse phase column, 85:15 H_2O–CH_3CN, 3.0 mL/min) as a white solid. Anal. Calcd for $C_{19}H_{19}N_2O_7SNa + 1.5H_2O$: C, 48.58; H, 4.72; N, 5.96. Found: C, 48.56; H, 4.63; N, 5.65. HRMS: $[M+H]^+$ 443.0885; $C_{19}H_{19}N_2O_7SNa$ + H requires 443.0889. ^{1}H NMR (300 MHz, MeOD): δ 2.42, 2.48* (1H, dd, $J_{6'a,5'}$ = 8.1/7.2*, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.54, 2.60* (1H, dd, $J_{6'b,5'}$ = 6.3/6.0*, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.34 (3H, s, OMe), 3.61, 3.63* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.75, 3.77* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.82, 3.85* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.03, 4.19* (1H, dd, $J_{5',6'a}$ = 6.3/6.9, $J_{5'6'b}$ = 6.6/6.9 Hz, H-5′), 4.29, 4.31* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.57, 4.58* (1H, s, H-2″), 5.51, 5.52* (1H, d, $J_{5,6}$ = 7.8 Hz, H-5), 7.37, 7.40* (1H, d, $J_{6',5'}$ = 7.8 Hz, H-6), 7.18–7.31 (3H, m, Ph), 7.50–7.55 (2H, m, Ph). ^{13}C NMR (75.5 MHz, MeOD): δ 31.7, 31.9* (C-6′), (C-1′ under MeOD peak), 50.4, 50.5* (OCH_3), 56.7, 57.0* (C-4′)†, 58.6, 58.8* (C-2″), 59.4, 59.6* (C-3′)†, 79.3, 79.8* (C-5′), 101.4, 101.5* (C-

5), 104.6, 104.8* (C-2′), 128.2, 129.3, 129.7, 129.8 (Ph), 141.1, 141.6* (*ipso*-Ph), 148.2, 148.3* (C-6), 153.2, 153.3* (C-2), 166.9 (C-4), 171.9, 172.0* (C-1″).

4.23. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium propionate)]-α-D-tagatofuranoside)-5-fluorouracil 27

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **19** gave **27** in 52% yield (HPLC: Phenomenex Aqua Semi-Preparative Column, Gradient: 6:94, CH_3CN–H_2O, 3.5 mL/min → 60:40, CH_3CN–H_2O, 4.0 mL/min → 6:94, CH_3CN–H_2O, 4.0 mL/min). HRMS: $[M+H]^+$ 399.0632; $C_{14}H_{16}FN_2O_7SNa$ + H requires 399.0638. ^1H NMR (300 MHz, MeOD): δ 1.37, 1.38* (3H, d, $J_{3'',2''}$ = 7.2 Hz, H-3″), 2.59, 2.67* (1H, dd, $J_{6'a,5'}$ = 8.1, $J_{6'a,6'b}$ = 13.5, H-6′a), 2.78, 2.86* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.36, 3.37* (3H, s, OMe), 3.39, 3.42* (1H, q, $J_{2'',3''}$ = 6.9 Hz, H-2″), 3.65, 3.66* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′)†, 3.79, 3.80* (1H, d, $J_{1'a,1'b}$ = 14.4 Hz, H-1′a), 3.90, 3.91* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4′)†, 4.27, 4.28* (1H, d, $J_{1'b,1'a}$ = 14.4 Hz, H-1′b), 4.33 (1H, dd, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 8.1 Hz, H-5′), 7.68, 7.69* (1H, d, $J_{6,F}$ = 6.6 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 19.0, 19.2* (C-3″), 31.6, 32.1* (C-6′), 49.5 (C-1′), (C-2″ under MeOD peak), 50.6 (OCH_3), 57.0, 57.1* (C-4′)†, 59.4, 59.5* (C-3′)†, 79.3, 79.5* (C-5′), 104.7, 104.8* (C-2′), 132.3 ($J_{6,F}$ = 34.0 Hz, C-6), 140.9 ($J_{5,F}$ = 231.0 Hz, C-5), 151.9 (C-2), 160.0 ($J_{4,F}$ = 25.7 Hz, C-4), 170.1 (C-1″).

4.24. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium butyrate)]-α-D-tagatofuranoside)-5-fluorouracil 28

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **20** gave **28** in 34% yield (HPLC: Phenomenex Aqua Semi-Preparative Column, 93:7 H_2O–CH_3CN, 4.0 mL/min). Anal. Calcd for $C_{15}H_{18}FN_2O_7SNa + 0.5H_2O$: C, 42.73; H, 4.54; N, 6.65. Found: C, 42.51; H, 4.43; N, 6.35. HRMS: $[M+H]^+$ 413.0793; $C_{15}H_{18}FN_2O_7SNa$ + H requires 413.0795. ^1H NMR (300 MHz, MeOD): δ 0.99, 1.00* (3H, t, $J_{4'',3''}$ = 7.5 Hz, H-4″), 1.72 (2H, dq, H-3″), 2.57, 2.66* (1H, dd, $J_{6'a,5'}$ = 8.4, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.77, 2.85* (1H, dd, $J_{6'b,5'}$ = 6.0, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.16, 3.18* (1H, t, $J_{2'',3''}$ = 8.4 Hz, H-2″), 3.36, 3.37* (3H, s, OMe), 3.64, 3.65* (1H, d, $J_{3',4'}$ = 3.0 Hz, H-3′)†, 3.78, 3.79* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 3.90, 3.91* (1H, d, $J_{4',3'}$ = 3.0 Hz, H-4′)†, 4.27, 4.28* (1H, d, $J_{1'b,1'a}$ = 14.1 H-1′b), 4.32, 4.34* (1H, m, H-5′), 7.66, 7.67* (1H, d, $J_{6,F}$ = 6.6 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 12.6, 12.7* (C-4″), 27.2, 27.4* (C-3″), 31.5, 32.3* (C-6′), 49.5 (C-1′), 50.6 (OCH_3), 54.0, 54.8* (C-2″), 57.0, 57.1* (C-3′)†, 59.4, 59.5* (C-4′)†, 79.3, 79.5* (C-5′), 104.8, 104.9* (C-2′), 132.0, 132.4* (C-6), 139.5 (C-5), 142.5 (C-2), 152.2 (C-4), 180.1, 180.5* (C-1″).

4.25. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium-2-phenylacetate)]-α-D-tagatofuranoside)-5-fluorouracil 29

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **21** gave **29** in 66% yield (HPLC: Phenomenex Aqua Semi-Preparative Column, 90:10 H_2O–CH_3CN, 4.0 mL/min). HRMS: $[M+H]^+$ 461.0787; $C_{19}H_{18}FN_2O_7$-SNa + H requires 461.0795. ^1H NMR (300 MHz, MeOD): δ 2.39, 2.47* (1H, dd, $J_{6'a,5'}$ = 8.7, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.56, 2.62* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.34 (3H, s, OMe), 3.61, 3.64* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′), 3.74, 3.75* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 3.83, 3.88* (1H, dd, $J_{4',5'}$ = 0.6, $J_{4',3'}$ = 2.7 Hz, H-4′), 4.02, 4.19* (1H, ddd, $J_{5',4'}$ = 0.6, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 8.7 Hz, H-5′), 4.25, 4.26* (1H, d, $J_{1'b,1'a}$ = 14.1 H-1′b), 4.56, 4.57* (1H, s, H-2″), 7.16–7.31 (3H, m, Ph), 7.48–7.54 (2H, m, Ph), 7.59, 7.60* (1H, d, $J_{6,F}$ = 6.3 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 31.5, 31.9* (C-6′), 49.5 (C-1′), 50.5, 50.6* (OCH_3), 56.7, 57.0* (C-4′), 58.6, 58.9* (C-2″), 59.3, 59.7* (C-3′), 79.2, 79.5* (C-5′), 104.6, 104.8* (C-2′), 128.2, 128.3, 129.3, 129.7, 129.8 (Ph), 131.9, 132.4* ($J_{6,F}$ = 33.2 Hz, C-6), 141.0 ($J_{5,F}$ = 231.0 Hz, C-5), 141.1, 141.5* (*ipso*-Ph), 152.1 (C-2), 160.5 (C-4), 177.2, 177.6* (C-1″).

4.26. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium butyrate)]-α-D-tagatofuranoside)-cytosine 30

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **22** gave **30** in 33% yield (HPLC: Phenomenex Aqua Semi-Preparative Column, 90:10 H_2O–CH_3CN, 4.0 mL/min). Anal. Calcd for $C_{15}H_{20}N_3O_6SNa + 2.5H_2O$: C, 41.07; H, 5.74; N, 9.58. Found: C, 41.35; H, 5.30; N, 9.22. HRMS: $[M+H]^+$ 394.1050; $C_{15}H_{20}N_3O_6SNa$ + H requires 394.1049. ^1H NMR (300 MHz, MeOD): δ 0.99 (3H, t, $J_{4'',3''}$ = 7.5 Hz, H-4″), 1.54–1.89 (2H, m, H-3″), 2.58, 2.65* (1H, dd, $J_{6'a,5'}$ = 7.8, $J_{6'a,6'b}$ = 13.5 Hz, H-6′a), 2.76, 2.81* (1H, dd, $J_{6'b,5'}$ = 6.3, $J_{6'b,6'a}$ = 13.5 Hz, H-6′b), 3.14, 3.19* (1H, dd, $J_{2'',3''a}$ = $J_{2'',3''b}$ = 6.3/6. 6* Hz, H-2″), 3.35, 3.36* (3H, s, OMe), 3.63, 3.64* (1H, d, $J_{3',4'}$ = 2.7 Hz, H-3′), 3.81, 3.82* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 3.84 (1H, m, H-4′), 4.26, 4.28* (1H, ddd, $J_{5',4'}$ = 0.6, $J_{5',6'b}$ = 6.3, $J_{5',6'a}$ = 7.2 Hz, H-5′), 4.36, 4.37* (1H, d, $J_{1'b,1'a}$ = 14.1 Hz, H-1′b), 5.81, 5.82* (1H, d, $J_{5,6}$ = 7.2 Hz, H-5), 7.45, 7.46* (1H, d, $J_{6,5}$ = 7.2 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 12.6, 12.7* (C-4″), 27.2, 27.3* (C-3″), 31.5, 32.4* (C-6′), 50.4 (C-1′), 50.1 (OCH_3), 54.0, 54.8* (C-2″), 56.8, 56.9* (C-4′)†, 59.6 (C-3′)†, 79.1, 79.5* (C-5′), 95.2 (C-5), 105.1 (C-2′), 148.4, 148.5 (C-6), 159.4 (C-2), 168.0 (C-4), 180.1, 180.5* (C-1″).

4.27. 1-(Methyl 3,4-anhydro-6-thio-6-[2′-(sodium-2-phenylacetate)]-α-D-tagatofuranoside)-cytosine 31

The title compound was prepared in a similar manner to that described in Section 4.20. De-esterification of **23** gave **31** in 5% yield (HPLC: Phenomenex Aqua Semi-Preparative Column, 80:20 H_2O–CH_3CN, 3.5 mL/min). HRMS: $[M+H]^+$ 442.1039; $C_{19}H_{20}N_3O_6SNa$ + H requires 422.1049. ^1H NMR (300 MHz, MeOD): δ 2.43, 2.47* (1H, dd, $J_{6'a,5'}$ = 7.2, $J_{6'a,6'b}$ = 13.5, H-6′a), 2.51, 2.55* (1H, dd, $J_{6'b,5'}$ = 6.6, $J_{6'b,6'a}$ = 13.5, H-6′b), 3.31, 3.33* (3H, s, OMe), 3.68, 3.69* (1H, d, $J_{3',4'}$ =

2.7 Hz, H-3′)†, 3.78, 3.79* (1H, d, $J_{1'a,1'b}$ = 14.1 Hz, H-1′a), 3.81, 3.83* (1H, d, $J_{4',3'}$ = 2.7 Hz, H-4)†, 4.01, 4.13* (1H, dd, $J_{5',6'b}$ = 6.6, $J_{5',6'a}$ = 7.2 Hz, H-5′), 4.37, 4.38* (1H, d, $J_{1'b,1'a}$ = 14.1 Hz, H-1′b), 4.72 (H-2″ not seen), 5.78, 5.80* (1H, d, $J_{5,6}$ = 7.2 Hz, H-5), 7.22–7.52 (5H, m, Ph), 7.25, 7.40* (1H, d, $J_{6,5}$ = 7.2 Hz, H-6). ^{13}C NMR (75.5 MHz, MeOD): δ 31.6, 31.9* (C-6′), 50.4 (C-1′), 50.7, 50.8* (OCH_3), 56.6 (C-2″), 58.4, 58.7* (C-4)†, 59.5 (C-3)†, 78.8, 79.3* (C-5′), 95.5 (C-5), 104.7, 104.9* (C-2′), 128.5, 129.4, 129.5 (Ph), 140.9 (*ipso*-Ph), 148.5 (C-6), 159.3 (C-2), 167.7 (C-4), 177.3 (C-1″).

4.28. Methyl 6-*S*-(methyl-3,4-anhydro-6-thio-β-D-tagatofuranoside)-3,4-anhydro-6-thio-β-D-tagatofuranoside 36

LRMS: $[M+Na]^+$ 561.0; $C_{16}H_{26}O_{12}S_4Na$ requires 561.0. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (2H, d, $J_{6/6',5}$ = 6.9 Hz, H-6/6′), 3.08 (3H, s, OMs), 3.51 (3H, s, OCH_3), 3.80 (1H, d, $J_{3,4}$ = 2.8 Hz, H-3), 3.90 (1H, dd, $J_{4,3}$ = 2.8 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 4.13 (1H, d, $J_{1,1'}$ = 11.0, H-1), 4.30 (1H, d, $J_{1',1}$ = 11.0 Hz, H-1′), 4.31 (1H, dd, $J_{5,4}$ = 0.8, $J_{5,6}$ = $J_{5,6'}$ = 4.8 Hz, H-5).

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