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A novel method for the synthesis of 4′-thiopyrimidine nucleosides using hypervalent iodine compounds

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The coupling reactions of cyclic sulfides with a silylated pyrimidine nucleobase using a hypervalent iodine reagent were investigated. The reaction of silylated uracil with cyclic sulfide **12** using PhI=O gave the desired β-anomer **14** in moderate yield. 4′-Thiouridine (**22**) was obtained by deprotection of **14**.

Introduction

Nucleoside antimetabolites occupy a pivotal position in the fields of anticancer and antiviral agents.[1] Recently, it has been reported that certain 4′-thionucleosides, in which the oxygen atom in the furanose ring is replaced by a sulfur atom, exhibit potent antiviral[2–5] and anticancer activities.[6–8] In addition, they have inherent properties such as a more stable glycosidic linkage and increased metabolic stability.[9,10] For example, 4′-thio-BVDU[3] has a level of antiviral activity equivalent to that of BVDU[11] and also shows resistance to the hydrolysis reaction by pyrimidine phosphorylase.[12] Therefore, there has been much effort to synthesize and evaluate new nucleoside analogues.

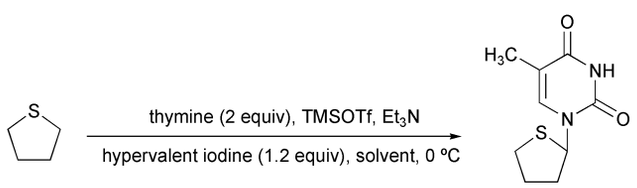
In general, thionucleoside derivatives have been synthesized by classical glycosidation of a nucleobase with the corresponding thiosugar, although the stereoselectivity of such thioglycosidation is not satisfactory even with the assistance of neighboring C-2 acyloxy group participation.[13–15] As an alternative method, O'Neil and Hamilton reported the synthesis of thionucleosides through the Pummerer reaction in 1992.[16] Stereoselective synthesis of thionucleoside derivatives using the Pummerer reaction has also been reported.[17–19] Very recently, stereoselective synthesis of the β-anomer of 4′-thionucleosides based on electrophilic addition to 4-thiofuranoid glycals has also been reported.[20]

Hypervalent iodine reagents have been extensively used in organic syntheses because of their low toxicity, ready availability and easy handling.[21] These reagents have been used mainly for C–C bond formation and for the oxidation of alcohols, phenols and sulfides. Although a few examples of C–N bond formation using these reagents have been reported, they are limited to cases of the introduction of an azido group by azidoiodane generated *in situ* from PhIO–$TMSN_3$ and the intramolecular cyclization of an imine nitrogen atom to the activated hydrazone.[21b] Interestingly, Kita and co-workers have reported the direct α-azidation of cyclic sulfides using a PhIO–$TMSN_3$ reagent system.[22] Their paper prompted us to initiate a study on application to nucleoside chemistry, and on the properties of hypervalent iodine reagents, such as the oxidizability of hypervalent iodine compounds and the leaving group ability of the phenyliodonio group, which have led us to explore thioglycosidation.

In this paper, we present the results of a study on the novel synthesis of 4′-thionucleoside using hypervalent iodine reagents in which the generation of a thionium cation is a key step.

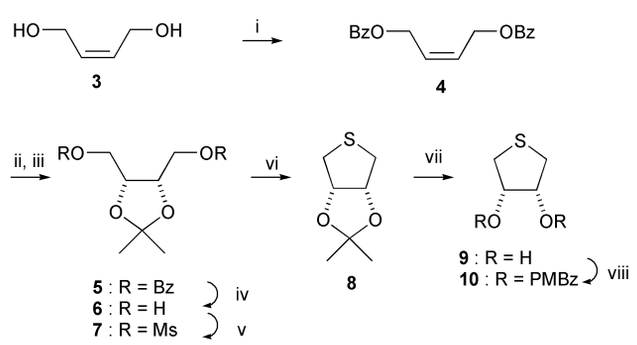
Results and discussion

In order to investigate effective thioglycosidation, commercially available tetrahydrothiophene (**1**) and thymine were selected as model compounds. Some hypervalent iodine reagents were used in preliminary experiments (Scheme 1, entries 1–4 in Table 1). Among them, [bis(trifluoroacetoxy)iodo]benzene gave 1-(tetrahydrothiophen-2-yl)thymine (**2**) in the highest yield. This seems to be due to the oxidizability and solubility of hypervalent iodine compounds. In order to optimize the reaction conditions, the mole ratios of trimethylsilyl trifluoromethansulfonate (TMSOTf) and triethylamine to **1** were varied (entries 4–8 in Table 1). When 6 equivalent moles of TMSOTf and triethylamine were used, the product was effectively obtained in 80% yield (entry 8 in Table 1). As for the solvents used, dichloromethane gave the best yield. Thus, it was found that the position adjacent to the sulfur atom on the thiophene ring was activated and that a C–N bond was subsequently formed.



Scheme 1

In the coupling of a nucleobase with a thiosugar, the control of stereo- and regio-selectivities is essential. To investigate the stereochemistry of the coupling reaction, di- and tri-substituted tetrahydrothiophenes (**10** and **12**) were used as thiosugar analogues. For the preparation of compound **10**, starting material *cis*-2-butene-1,4-diol (**3**) was converted to butene dibenzoate (**4**) and subsequently *O*-isopropylidene derivatives (**5**–**7**) (Scheme 2). *O*-Isopropylidene mesylate **7** was treated with



Scheme 2 *Reagents and conditions*: i) BzCl, Et_3N, CH_2Cl_2, 0 °C, 93%; ii) OsO_4, NMO, acetone, H_2O; iii) 2,2-dimethoxypropane, TsOH, acetone, 2 steps 86%; iv) NaOMe, MeOH, 96%; v) MsCl, pyridine, 76%; vi) Na_2S, DMF, 100 °C, 64%; vii) 80% AcOH, reflux, 87%; viii) PMBzCl, pyridine, 93%.

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Table 1 Coupling reaction of tetrahydrothiophene (**1**) with thymine (2 equiv.) at 0 °C for 12 h

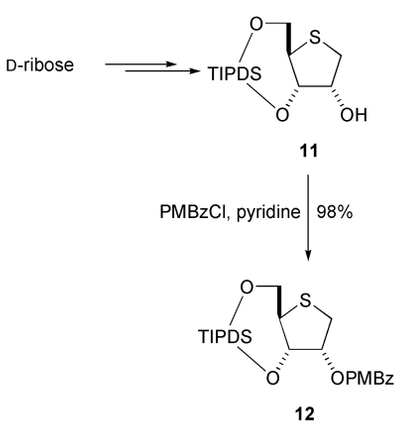
Entry	TMSOTf (equiv.)	Et_3N (equiv.)	Hypervalent iodine (1.2 equiv.)	Solvent	Yield of **2** (%)
1	8	8	PhI=O	CH_2Cl_2	5
2	8	8	$PhI(OAc)_2$	CH_2Cl_2	10
3	8	8	PhI(OH)OTs	CH_2Cl_2	20
4	8	8	$PhI(OCOCF_3)_2$	CH_2Cl_2	42
5	6	4	$PhI(OCOCF_3)_2$	CH_2Cl_2	0
6	4	6	$PhI(OCOCF_3)_2$	CH_2Cl_2	29
7	4	4	$PhI(OCOCF_3)_2$	CH_2Cl_2	63
8	6	6	$PhI(OCOCF_3)_2$	CH_2Cl_2	80
9	6	6	$PhI(OCOCF_3)_2$	CH_3CN	52
10	6	6	$PhI(OCOCF_3)_2$	Toluene	45
11	6	6	$PhI(OCOCF_3)_2$	THF	62
12	6	6	$PhI(OCOCF_3)_2$	CH_2Cl_2–toluene	54

Table 2 Coupling reaction of *meso*-3,4-di-*O*-*p*-methoxybenzoylthiolane-3,4-diol (**10**) with thymine using Method A

Entry	Thymine (equiv.)	TMSOTf (equiv.)	Et_3N (equiv.)	Yield of **13**[a] (%)	β : α[b]
1	2	6	6	63	3 : 1
2	2	8	8	35	3 : 1
3	3	8	8	48	2 : 1
4	2	6	3 + 3	65	4 : 1
5	3	3	4 + 4	65	5 : 1

[a] Isolated yields of the anomer mixture. [b] Estimated from ^{1}H NMR spectroscopy.

sodium sulfide to give *O*-isopropylidenethiolanediol **8**, which ultimately led to the formation of **10**. Tri-substituted tetrahydrothiophene **12** was prepared, in several steps, from D-ribose according to the reported procedure (Scheme 3).[23]



Scheme 3

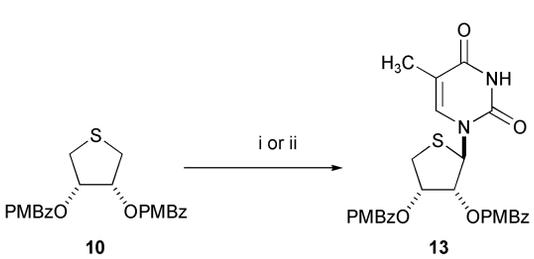
First, the reaction of thymine with **10** using hypervalent iodine was examined (Scheme 4). The results are summarized in Table 2 (see Method A in the Experimental section). Under the conditions used for the synthesis of **2**, the reaction gave **13** with the anomer ratio β : α = 3 : 1 in moderate yield. The reactions were carried out with various mole ratios of TMSOTf and triethylamine to thymine, but with lower isolated yields (entries 2 and 3 in Table 2). These decreased yields seemed to be due to the formation of a thiophene derivative as a by-product. Although such thiophene formation has been observed in Pummerer-type reactions, the formation of the by-product has been prevented by adding triethylamine in two portions.[19]

Similarly triethylamine was added twice in the reaction of thymine with **10**. Interestingly, the anomer ratio β : α was improved up to 5 : 1, whereas the yield of the product was not improved (entries 4 and 5 in Table 2).

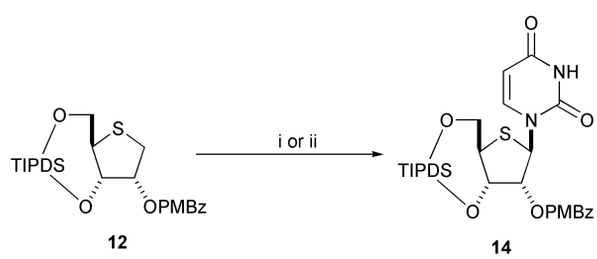
From the above results, it was deduced that the generation of a Pummerer-type intermediate is a key step. Therefore, to effectively generate the intermediate, the order of addition of reagents and substrate was considered, that is, a silylated nucleobase was added to the initially formed Pummerer-type intermediate, which arose from the reaction of iodosobenzene and TMSOTf with the thiophene derivative (Scheme 4) (see Method B in the Experimental section). Surprisingly, only the desired β-anomer **13** was obtained in 61% yield (Scheme 4; in the case of reagent ii).

Next, to investigate the regio- and stereo-selectivities of this coupling reaction, the reaction of uracil with tri-substituted tetrahydrothiophene **12** was examined, since uracil and cytosine are components of ribonucleosides. The reactions of uracil with **12** were carried out at various temperatures according to Method A, giving a 5 : 1 anomer mixture of **14** in 20–55% yields (Scheme 5, Table 3). When the reaction was carried out at 0 °C, the best result was obtained (entry 2 in Table 3). Furthermore, to improve the yield and stereoselectivity, the reaction was carried out at 0 °C according to Method B. The reaction proceeded stereoselectively to give only β-anomer **14** in 53% yield (Scheme 5).

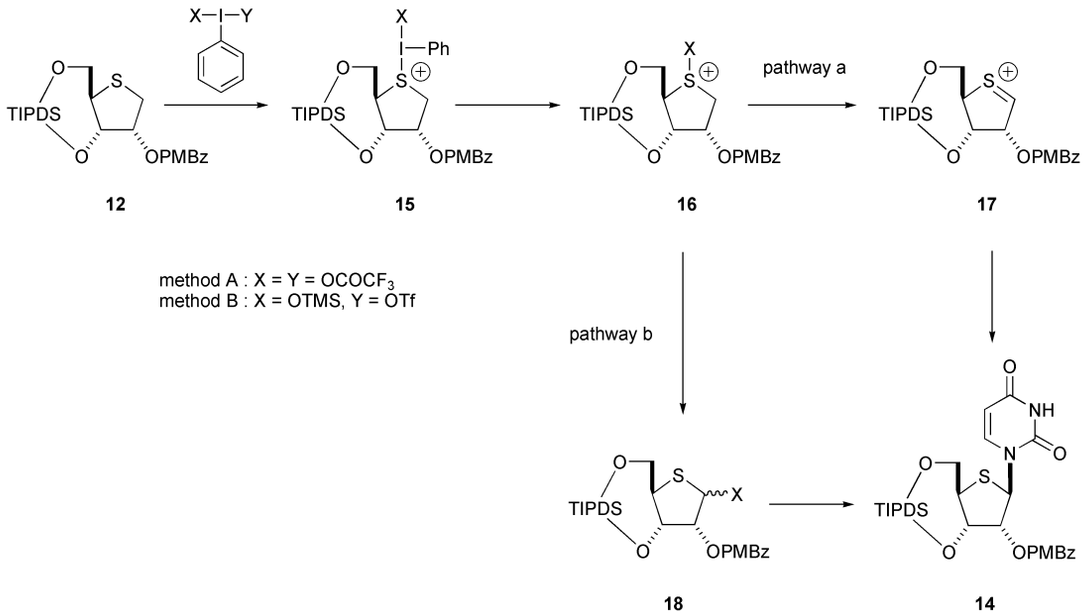
This high β-anomer selectivity seems to be based on the generation of thionium cation **16** (X = OTMS) as well as one of



Scheme 4 *Reagents and conditions*: i) thymine, TMSOTf, Et_3N, $PhI(OCOCF_3)_2$, CH_2Cl_2, 0 °C; ii) PhI=O, TMSOTf, Et_3N, thymine, CH_2Cl_2, 0 °C, 61%.



Scheme 5 *Reagents and conditions*: i) uracil, TMSOTf, Et_3N, $PhI(OCOCF_3)_2$, CH_2Cl_2, 0 °C; ii) PhI=O, TMSOTf, Et_3N, uracil, CH_2Cl_2, 0 °C, 53%.



Scheme 6 Reaction pathways.

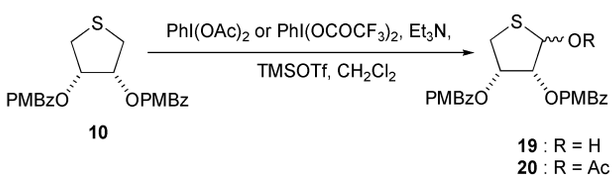
Table 3 Coupling reaction of a 4-thio-D-ribitol derivative (**12**) with uracil using Method A

Entry	Solvent	Temp./°C	Yield of **14** (%)[a]
1	CH_2Cl_2	−40	48
2	CH_2Cl_2	0	55
3	CH_2Cl_2	rt	50
4	$ClCH_2CH_2Cl$	Reflux	20

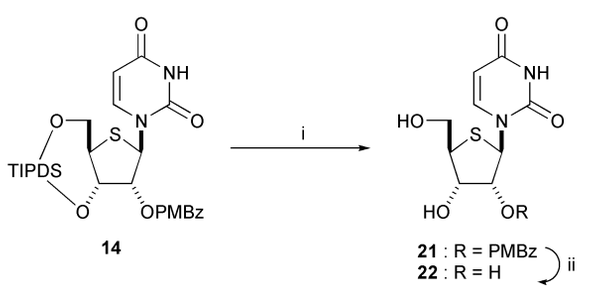
[a] Isolated yields of the anomer mixture.

the Pummerer reactions (Scheme 6).[17–20] The reaction would be initiated by the attack of the hypervalent iodine on the sulfur atom, and iodobenzene and a proton at the 2-position of the tetrahydrothiophene ring might subsequently be regioselectively eliminated to generate a thionium cation **17** (pathway **a**). The generated thionium cation **17** is attacked by a nucleobase from the favorable β-face due to neighboring group participation of the 3-*O*-PMBz group to give only the β-anomer **14**. Thus, the coupling reaction in Method B showed high stereoselectivity in comparison with that in Method A. The difference between the stereoselectivities of the coupling reactions in Methods A and B seems to be due to the cyclic sulfonium salt (**15** or **16**) reacting *via* two pathways, **a** and **b**, *i.e.*, *via* a thionium cation **17** and thiosugar **18**, respectively. In the case of pathway **a**, thionium cation **17** is subjected to neighboring group participation by the 3-*O*-PMBz group, which is similar to the pathway of the Pummerer reaction, to give the β-anomer. On the other hand, in pathway **b**, the generated thiosugar **18** reacts with a nucleobase to give a mixture of α- and β-nucleoside due to classical glycosidation. It is well known that the stereoselectivity in classical glycosidation of thiosugar is not satisfactory even with the assistance of neighboring C-2 acyloxy group participation, though the reason is not clear.[13–15] In Method A, the generation of thiosugar **18** was suggested by the fact that the reaction of disubstituted tetrahydrothiophene **10** with $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$ gave thiosugar derivatives (**19** or **20**) in the absence of a nucleobase under the conditions used in method A (Scheme 7). Thus, it seems that both pathways **a** and **b** occur in the reaction in method A, but only pathway **a** in the reaction in Method B.

The resulting silylated thiouridine derivative **14** was treated with NH_4F and then deprotected using methanolic ammonia to afford a free 4′-thiouridine (**22**) in 66% yield (Scheme 8). The



Scheme 7



Scheme 8 *Reagents and conditions*: i) NH_4F, MeOH; ii) NH_3–MeOH, 2 steps 66%.

structure of **22** was confirmed by comparison of the analytical data with those previously reported.[19,24]

In conclusion, this stereo- and regio-selective thioglycosidation using a hypervalent iodine reagent provides a useful method for the coupling of a thiosugar with a nucleobase. In addition, the C–N bond formation that occurs using this reagent is the first such example in an intermolecular reaction, and so this method might be used as a new tool in synthetic chemistry. Further studies are in progress.

Experimental section

All melting points were determined on a Yamato melting point apparatus (model MP-2) and are uncorrected. NMR spectra were recorded on a JEOL JNM-LA-300 spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS (0.0 ppm) as internal standard. Coupling constants, J, are given in Hz. MS spectra were obtained on a JEOL JMS-HX110 and JEOL JMS-700TZ. Column chromatography was conducted using silica gel (Merck, Silica gel 60, 70–230 mesh).

1-(Tetrahydrothiophen-2-yl)thymine (2)

To a suspension of thymine (126 mg, 1.0 mmol) in CH_2Cl_2 (2 cm^3) were added Et_3N (0.42 cm^3, 3.0 mmol) and TMSOTf

(0.50 cm^3, 3.0 mmol), and the mixture was stirred vigorously at room temperature for 1 h under an argon atmosphere. The mixture was then cooled in an ice–water bath, and tetrahydrothiophene (**1**) (0.44 cm^3, 0.5 mmol) and $PhI(OCOCF_3)_2$ (129 mg, 0.6 mmol) were added. The resulting mixture was stirred for 12 h, and the reaction was quenched by addition of ice. The mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (1 : 1), to give **2** (86 mg, 80%) as a colourless solid. Mp 169–173 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 1.96 (3 H, s), 1.92–2.16 (3 H, m), 2.44–2.33 (1 H, m), 2.98 (1 H, dt, *J* 6.4 and 10.5), 3.21 (1 H, dt, *J* 6.4 and 10.5), 6.32 (1 H, dd, *J* 5.2 and 6.7), 7.55 (1 H, d, *J* 1.3), 8.98 (1 H, br s, NH); δ_C(75 MHz; $CDCl_3$) 12.7, 29.2, 33.5, 38.1, 63.8, 110.9, 136.5, 150.9, 163.8; *m*/*z* (FAB) 213.0682 (MH^+. $C_9H_{13}N_2O_2S$ requires 213.0619). Anal. calcd. for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20; S, 15.11. Found: C, 50.92; H, 5.63; N, 13.11; S, 15.14%.

cis-1,4-Di-*O*-benzoyl-2-butene-1,4-diol (4)

To a solution of *cis*-2-butene-1,4-diol (**3**) (4.0 g, 46 mmol) in CH_2Cl_2 (200 cm^3) were added Et_3N (19 cm^3, 138 mmol) and benzoyl chloride (16 cm^3, 138 mmol) at 0 °C under an argon atmosphere, and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of ice, and the reaction mixture was partitioned between ether and water. The separated organic layer was washed with water and then with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (7 : 1), to give **4** (12.7 g, 93%) as a colourless solid. Mp 60–63 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 5.01 (4 H, m), 5.95 (2 H, m), 7.41–7.59 (6 H, m), 8.04–8.07 (4 H, m); δ_C(75 MHz; $CDCl_3$) 60.5, 128.4, 129.6, 130.0, 133.0, 166.3; *m*/*z* (EI) 296.1024 (MH^+. $C_{18}H_{16}O_4$ requires 296.1049). Anal. calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.07; H, 5.67%.

meso-1,4-Di-*O*-benzoyl-2,3-*O*-isopropylidenebutane-1,2,3,4-tetrol (5)

To a solution of **4** (8.0 g, 24 mmol) in acetone (100 cm^3) were added NMO (4.0 g, 34 mmol) and a 0.02 M solution of OsO_4 in *t*-BuOH (16 cm^3, 0.3 mmol) at room temperature under an argon atmosphere, and the resulting mixture was stirred at room temperature for 12 h. The mixture was diluted with ethyl acetate and washed with saturated $Na_2S_2O_4$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone (500 cm^3), and then *p*-TsOH (500 mg) and acetone dimethyl acetal (50 cm^3) were added. The mixture was stirred at room temperature for 4 h and neutralized by saturated sodium bicarbonate. The solvent was evaporated under reduced pressure. The residue was partitioned between ether and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (7 : 1), to give **5** (7.6 g, 86%) as colourless needles. Mp 108–109 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 1.43 (3 H, s), 1.53 (3 H, s), 4.44–4.64 (6 H, m), 7.40–7.60 (6 H, m), 8.04–8.08 (4 H, m); δ_C(75 MHz; $CDCl_3$) 25.3, 27.7, 62.9, 74.7, 109.5, 128.4, 129.6, 129.7, 133.2, 166.2; *m*/*z* (EI) 355.1196 ($M^+ - CH_3$. $C_{20}H_{19}O_6$ requires 355.1182). Anal. calcd. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.14; H, 6.13%.

meso-2,3-*O*-Isopropylidenebutane-1,2,3,4-tetrol (6)

To a solution of **5** (6.0 g, 16 mmol) in methanol (150 cm^3) was added 28% sodium methoxide (1 cm^3) at room temperature, and the mixture was stirred at room temperature for 30 min. The mixture was neutralized with saturated NH_4Cl and partitioned between ether and water. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with 5% ethanol in $CHCl_3$, to give **6** (2.5 g, 96%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 1.38 (3 H, s), 1.47 (3 H, s), 2.85 (2 H, br s, OH), 3.77 (4 H, m), 4.30 (2 H, m); δ_C(75 MHz; $CDCl_3$) 25.4, 27.8, 61.0, 76.8, 108.7; *m*/*z* (FAB) 163.0968 (MH^+. $C_7H_{15}O_4$ requires 163.0970). Anal. calcd. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.84; H, 8.61%.

meso-2,3-*O*-Isopropylidene-1,4-di-*O*-(methanesulfonyl)butane-1,2,3,4-tetrol (7)

To a solution of **6** (2.0 g, 12 mmol) in pyridine (100 cm^3) was added methanesulfonyl chloride (2.8 cm^3, 36 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of ice, and the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column, eluted with hexane–AcOEt (1 : 1), to give **7** (2.9 g, 76%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 1.39 (3 H, s), 1.49 (3 H, s), 3.09 (6 H, s), 4.29–4.37 (4 H, m), 4.48 (2 H, m); δ_C(75 MHz; $CDCl_3$) 25.3, 27.7, 38.0, 66.7, 74.4, 110.4; *m*/*z* (EI) 303.0230 ($M^+ - CH_3$. $C_8H_{15}O_8S_2$ requires 303.0208).

meso-3,4-*O*-Isopropylidenethiolane-3,4-diol (8)

To a solution of **7** (3.1 g, 9.7 mmol) in DMF (100 cm^3) was added $Na_2S{\cdot}9H_2O$ (2.8 g, 11.6 mmol), and the resulting mixture was stirred at 100 °C for 24 h under an argon atmosphere. The mixture was diluted with ether and washed with water (twice) and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (7 : 1), to give **8** (977 mg, 64%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 1.33 (3 H, s), 1.52 (3 H, s), 2.87 (4 H, m), 4.85 (2 H, m); δ_C(75 MHz; $CDCl_3$) 24.6, 26.1, 38.6, 82.9, 110.9; *m*/*z* (EI) 160.0565 (M^+. $C_7H_{12}O_2S$ requires 160.0558). Anal. calcd. for $C_7H_{12}O_2S$: C, 52.47; H, 7.55. Found: C, 52.27; H, 7.42%.

meso-Thiolane-3,4-diol (9)

To a solution of **8** (790 mg, 4.9 mmol) in methanol (50 cm^3) was added 80% acetic acid, and the mixture was refluxed for 8 h. The solvent was removed under reduced pressure. The residue was purified on a silica gel column, eluted with hexane–AcOEt (1 : 3), to give **9** (512 mg, 87%) as a colourless solid. Mp 69–71 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 2.39 (2 H, br s, OH), 2.82 (2 H, dd, *J* 5.1 and 11.2), 3.03 (2 H, dd, *J* 5.6 and 11.2), 4.30 (2 H, dd, *J* 5.1 and 5.6); *m*/*z* (EI) 120.0246 (M^+. $C_4H_8O_2S$ requires 120.0245). Anal. calcd. for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.02; H, 6.76; S, 26.71%.

meso-3,4-Di-*O*-*p*-methoxybenzoylthiolane-3,4-diol (10)

To a solution of **9** (249 mg, 2.1 mmol) in pyridine (15 cm^3) was added *p*-methoxybenzoyl chloride (1.1 g, 6.6 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of ice, and the reaction mixture was partitioned between ether and water. The separated organic layer was washed with water and then with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (3 : 1), to give **10** (757 mg, 93%) as a colourless solid. Mp 112–115 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 3.30 (2 H, dd, *J* 5.7 and 11.2), 3.14 (2 H, dd, *J* 5.3 and 11.2), 3.85 (6 H, s), 5.71 (2 H, m), 6.88 (4 H, d, *J* 8.8), 7.95 (4 H, d, *J* 8.8); δ_C(75 MHz;

$CDCl_3$) 31.1, 55.4, 74.7, 113.7, 122.0, 131.8, 163.6, 165.3; *m*/*z* (FAB) 389.1051 (MH^+. $C_{20}H_{21}O_6S$ requires 389.1059). Anal. calcd. for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.65; H, 5.27%.

1,4-Anhydro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (11)

The title compound was prepared from D-ribose according to the reported procedure.[23] δ_H(300 MHz; $CDCl_3$) 0.95–1.09 (28 H, m), 2.64 (1 H, m), 2.84 (1 H, m), 2.84 (1 H, dd, *J* 1.6 and 12.1), 3.03 (1 H, ddd, *J* 1.5, 4.7 and 12.1), 3.50 (1 H, ddd, *J* 3.3, 4.7 and 8.3), 3.90 (1 H, dd, *J* 4.7 and 12.4), 4.04 (1 H, dd, *J* 3.3 and 12.4), 4.23 (1 H, dd, *J* 3.9 and 8.3), 4.33 (1 H, m); δ_C(75 MHz; $CDCl_3$) 12.6, 12.7, 13.1, 13.3, 13.4, 17.1, 17.2, 17.3, 17.4, 32.4, 49.2, 61.0, 74.4, 77.5; *m*/*z* (FAB) 393.1972 (MH^+. $C_{17}H_{37}O_4SSi_2$ requires 393.1952). Anal. calcd. for $C_{17}H_{36}O_4SSi_2$: C, 51.99; H, 9.24; S, 8.17. Found: C, 51.76; H, 9.00; S, 8.26%.

1,4-Anhydro-2-*O*-(*p*-methoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-ribitol (12)

To a solution of **11** (730 mg, 1.9 mmol) in pyridine (35 cm^3) was added *p*-methoxybenzoyl chloride (0.65 cm^3, 3.8 mmol) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with ice, and the mixture was partitioned between ethyl acetate and water. The separated organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (15 : 1), to give **12** (980 mg, 98%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 1.11–0.87 (28 H, m), 2.90 (1 H, d, *J* 12.5), 3.23 (1 H, dd, *J* 4.5 and 12.5), 3.66 (1 H, ddd, *J* 3.0, 3.2 and 9.5), 3.87 (3 H, s), 3.96 (1 H, dd, *J* 3.2 and 12.4), 4.10 (1 H, dd, *J* 3.0 and 12.4), 4.34 (1 H, dd, *J* 3.8 and 9.5), 5.73 (1 H, dd, *J* 3.8 and 4.5), 6.90–6.95 (2 H, m), 8.00–8.05 (2 H, m); δ_C(75 MHz; $CDCl_3$) 12.6, 12.7, 13.2, 13.3, 13.4, 17.0, 17.1, 17.2, 17.3, 17.4, 31.0, 496, 55.4, 59.9, 75.5, 75.7, 113.6, 122.7, 131.8, 163.4, 165.6; *m*/*z* (FAB) 527.2305 (MH^+. $C_{25}H_{43}O_6SSi_2$ requires 527.2241). Anal. calcd. for $C_{25}H_{43}O_6SSi_2$: C, 56.99; H, 8.04; S, 6.09. Found: C, 56.90; H, 8.00; N, 6.04%.

(2*R**, 3*R**, 4*S**)-1-(3,4-Di-*O*-*p*-methoxybenzoylthiolane-3,4-diol-2-yl)thymine (13)

Method A. To a suspension of thymine (66 mg, 0.52 mmol) in CH_2Cl_2 (2 cm^3) were added Et_3N (0.11 cm^3, 0.78 mmol) and TMSOTf (0.28 cm^3, 1.56 mmol) at room temperature under a nitrogen atmosphere. After the mixture had been stirred for 1 h, a clear solution was obtained. A solution of **10** (100 mg, 0.26 mmol) in CH_2Cl_2 (2 cm^3) was added to the mixture at 0 °C, and $PhI(OCOCF_3)_2$ (133 mg, 0.31 mmol) was then added in one portion. After stirring for 10 min, additional Et_3N (0.109 cm^3, 0.78 mmol) in CH_2Cl_2 (1 cm^3) was added dropwise to the reaction mixture. After the mixture had been stirred for 12 h, the reaction was quenched by addition of ice, and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (1 : 1), to give **13** (87 mg, 65%) as a colourless solid. Mp 239–242 °C (hexane–AcOEt); δ_H(300 MHz; $CDCl_3$) 2.00 (3 H, s), 3.23 (1 H, dd, *J* 2.6 and 12.5), 3.72 (1 H, dd, *J* 4.6 and 12.5), 3.83 (3 H, s), 3.88 (3 H, s), 5.62 (1 H, dd, *J* 3.9 and 7.9), 5.91 (1 H, m), 6.66 (1 H, d, *J* 7.9), 6.83–6.97 (4 H, m), 7.53 (1 H, s), 7.86–8.03 (5 H, m); δ_C(75 MHz; $CDCl_3$) 12.8, 32.9, 55.5, 61.5, 72.5, 77.5, 112.4, 113.7, 113.8, 120.7, 121.3, 131.9, 132.0, 135.4, 150.5, 162.8, 163.7, 163.8, 164.9, 165.0; *m*/*z* (FAB) 513.1360 (MH^+. $C_{25}H_{25}N_2O_8S$ requires 513.1332). Anal. calcd. for $C_{25}H_{24}N_2O_8S$: C, 58.59; H, 4.72; N, 5.47; S, 6.26. Found: C, 58.41; H, 4.77; N, 5.36; S, 6.10%.

Method B. To a suspension of thymine (66 mg, 0.52 mmol) in CH_2Cl_2 (2 cm^3) were added Et_3N (0.14 cm^3, 1.04 mmol) and TMSOTf (0.28 cm^3, 1.56 mmol), and the mixture was stirred at room temperature for 1 h to afford a silylated thymine solution. To a solution of **10** (100 mg, 0.26 mmol) in CH_2Cl_2 (2 cm^3) were added iodosobenzene (133 mg, 0.31 mmol) and TMSOTf (0.94 cm^3, 0.52 mmol) at 0 °C. After stirring for 5 min, the silylated thymine solution was added to the mixture and Et_3N (0.14 cm^3, 1.04 mmol) was then added, and the resulting mixture was stirred for 12 h. The reaction was quenched by the addition of ice, and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (1 : 1), to give **13** (76 mg, 61%) as a colourless solid.

1-[2-*O*-(*p*-Methoxybenzoyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-β-D-ribofuranosyl]uracil (14)

Method B. To a suspension of uracil (45 mg, 0.4 mmol) in CH_2Cl_2 (2 cm^3) were added Et_3N (0.11 cm^3, 0.8 mmol) and TMSOTf (0.22 cm^3, 1.2 mmol), and the mixture was stirred at room temperature for 1 h to afford a silylated uracil solution. To a solution of **12** (105 mg, 0.2 mmol) in CH_2Cl_2 (2 cm^3) were added iodosobenzene (48 mg, 0.2 mmol) and TMSOTf (0.73 cm^3, 0.4 mmol) at 0 °C. After stirring for 5 min, the silylated uracil solution was added to the mixture and Et_3N (0.11 cm^3, 0.8 mmol) was then added, and the resulting mixture was stirred for 12 h. The reaction was quenched by addition of ice, and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (1 : 1), to give **14** (67 mg, 53%) as a yellow solid. Mp 89–93 °C (hexane–AcOEt). δ_H(300 MHz; $CDCl_3$) 0.89–1.15 (28 H, m), 3.72 (1 H, d, *J* 9.5), 3.87 (3 H, s), 4.05–4.17 (2 H, m), 4.44 (1 H, dd, *J* 3.9 and 9.5), 5.61 (1 H, d, *J* 3.9), 5.75 (1 H, dd, *J* 2.1 and 8.3), 6.00 (1 H, s), 6.93 (2 H, d, *J* 8.6), 8.02 (1 H, d, *J* 8.3), 8.20 (1 H, d, *J* 8.3), 8.82 (1 H, br s, NH); δ_C(75 MHz; $CDCl_3$) 12.5, 131.1, 13.2, 13.3, 16.8, 16.9, 17.0, 17.2, 17.3, 17.4, 50.9, 55.4, 57.9, 62.3, 71.6, 78.1, 102.3, 113.7, 122.0, 131.9, 139.0, 141.0, 150.0, 163.6, 1642; *m*/*z* (FAB) 637.2438 (MH^+. $C_{29}H_{45}N_2O_8SSi_2$ requires 637.2436). Anal. calcd. for $C_{29}H_{44}N_2O_8SSi_2$: C, 54.69; H, 6.96; N, 4.40; S, 5.03. Found: C, 54.45; H, 7.01; N, 4.18; S, 4.96%.

2,3-Di-*O*-*p*-methoxybenzoyl-4-thio-DL-erythrofuranose (19)

To a solution of **10** (50 mg, 0.13 mmol) in CH_2Cl_2 (2 cm^3) were added $PhI(OCOCF_3)_2$ (56 mg, 0.13 mmol) and TMSOTf (0.24 cm^3, 0.13 mmol) at 0 °C under a nitrogen atmosphere. After stirring for 15 min, a solution of Et_3N (0.18 cm^3, 0.13 mmol) in CH_2Cl_2 (1 cm^3) was added dropwise to the mixture, and the mixture was stirred for 2 h. The mixture was diluted with ethyl acetate and then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column, eluted with hexane–AcOEt (4 : 1), to give **19** (34 mg, 65%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 2.53 (1 H, d, *J* 5.3), 2.80 (0.25 H, d, *J* 11.6), 3.17 (1 H, dd, *J* 8.1 and 10.4), 3.31 (0.5 H, m), 3.59 (1 H, dd, *J* 6.6 and 10.4), 3.84 (3.75 H, s), 3.87 (3.75 H, s), 5.41 (0.25 H, m), 5.48 (1 H, dd, *J* 2.4 and 5.3), 5.66–5.74 (1.25 H, m), 5.86 (1 H, m), 5.97 (0.25 H, m), 6.83–6.95 (5 H, m), 7.87–8.08 (5 H, m); *m*/*z* (FAB) 405.0997 (MH^+. $C_{20}H_{21}O_7S$ requires 405.1009).

1-*O*-Acetyl-2,3-di-*O*-*p*-methoxybenzoyl-4-thio-DL-erythrofuranose (20)

This compound was prepared using $PhI(OAc)_2$ as the hypervalent iodine according to the procedure used for the prepar-

ation of **19**. Silica gel column chromatography (hexane–AcOEt = 1 : 1) gave **20** (62%) as a colourless syrup. δ_H(300 MHz; $CDCl_3$) 2.14 (3 H, s), 3.20 (1 H, dd, *J* 8.4 and 10.3), 3.48 (1 H, dd, *J* 6.6 and 10.3), 3.84 (3 H, s), 3.87 (3 H, s), 5.79 (1 H, ddd, *J* 3.5, 6.6 and 8.4), 5.85 (1 H, dd, *J* 2.0 and 3.5), 6.05 (1 H, d, *J* 2.0), 6.81–6.95 (4 H, m), 7.85–8.11 (4 H, m); *m*/*z* (FAB) 447.1143 (MH^+. $C_{22}H_{23}O_8S$ requires 447.1114).

1-(4-Thio-ß-D-ribofuranosyl)uracil (22)

To a solution of **14** (340 mg, 0.53 mmol) in methanol (10 cm^3) was added NH_4F (393 mg, 10.6 mmol), and the mixture was heated under reflux for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in methanolic ammonia (15 cm^3). The mixture was kept for 24 h at room temperature, and the solvent was removed under reduced pressure. The residue was purified on a silica gel column, eluted with $CHCl_3$–EtOH (5 : 1), to give **22** (90 mg, 66%) as a colourless solid. Mp 195–196 °C (lit.[19,24] mp 195–196 °C) ($CHCl_3$–EtOH); δ_H(300 MHz; DMSO-d_6) 3.19 (1 H, ddd, *J* 2.4, 5.4 and 6.2), 3.52 (1 H, ddd, *J* 5.3, 5.4 and 11.2), 3.62 (1 H, ddd, *J* 5.3, 6.2 and 11.2), 4.02 (1 H, ddd, *J* 2.4, 2.8 and 3.5), 4.15 (1 H, ddd, *J* 3.5, 5.3 and 7.3), 5.18 (1 H, t, *J* 5.3), 5.26 (1 H, d, *J* 2.8), 5.48 (1 H, d, *J* 5.3), 5.67 (1 H, d, *J* 8.1), 5.89 (1 H, d, *J* 7.3), 7.99 (1 H, d, *J* 8.1), 11.31 (1H, br s, NH); δ_C(75 MHz; DMSO-d_6) 53.0, 62.3, 63.1, 73.0, 76.3, 102.1, 141.5, 151.1, 162.9; *m*/*z* (FAB) 261.0557 (MH^+. $C_9H_{13}N_2O_5S$ requires 261.0546).

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