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Synthesis of 1-(5,6-dihydro-2*H*-thiopyran-2-yl)uracil by a Pummerer-type thioglycosylation reaction: the regioselectivity of allylic substitution

Yuichi Yoshimura *, Yoshiko Yamazaki, Yukako Saito, Hiroki Takahata *

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

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ABSTRACT

1-(5,6-Dihydro-2*H*-thiopyran-2-yl)uracil derivatives, a new 4′-thio-D4-nucleoside analogue, were synthesized by reacting 5,6-dihydro-2*H*-thiopyran sulfoxide and persilylated uracil in a Pummerer-type thioglycosylation reaction. The reaction of 5-alkyl substituted dihydrothiopyran sulfoxide **7** only gave 1-(dihydrothiopyran-2-yl)uracil **9**. On the other hand, the reaction with a 5-siloxy substituted derivative of **7** resulted in a mixture of products with the uracil moiety at either the α- or the γ-position. The use of a prolonged reaction time resulted in the exclusive formation of the 4-substituted dihydrothiopyran derivative **10**. The result suggests that an equilibrium is operative in the formation of the α- and γ-adducts and that the latter should be more thermodynamically stable than the former. This conclusion was also supported by theoretical calculations.

1. Introduction

The search for new biologically active nucleosides is an important task for medicinal chemists especially for investigators who are attempting to develop antiviral drugs and antitumor agents. In previous studies, we reported on the design and synthesis of various nucleoside derivatives.[1,2] Among these, 4′-thionucleosides, which contain a sulfur atom in place of the oxygen of the furanose ring, are particularly interesting targets as both antiviral and antitumor agents.[2] We previously reported on the design and synthesis of a variety of 4′-thionucleosides that have antiviral and antineoplastic activities,[2] as represented by 4′-thioFAC **1**.[2b,e,i,j] As a part of our ongoing studies to identify new antiviral agents, we envisioned the synthesis of 1-(5,6-dihydro-2*H*-thiopyran-2-yl)cytosine **2**,[3] which was designed based on the known anti-HIV 4′-thionucleoside **3** (Chart 1).

In general, there are several problems associated with the synthesis of 4′-thionucloesides: (1) the construction of a 4-thiosugar skeleton, (2) the subsequent formation of a glycosidic bond between the 4-thiosugar portion and a nucleobase. As a solution for the second problem, we developed a Pummerer-type thioglycosylation reaction, in which the 4-thiosugar sulfoxide is directly coupled with a persilylated nucleobase.[2a,b,g,3,4] The method proved to be useful for producing 4′-thiocucleosides. As a result, it was

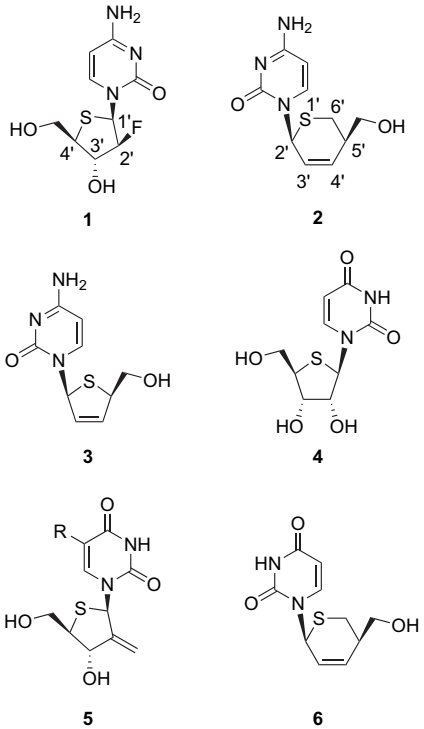

Chart 1.

* Corresponding authors. Tel.: +81 22 727 0145.
E-mail address: yoshimura@tohoku-pharm.ac.jp (Y. Yoshimura).

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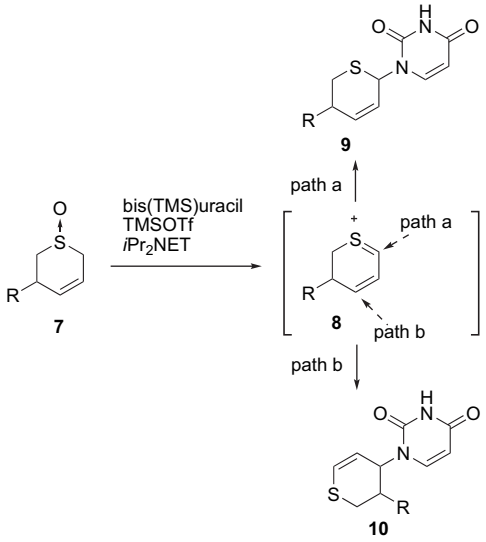
possible to prepare a variety of 4′-thionucleosides including the 4′-thioribonucleoside **4**[4] using the Pummerer-type thioglycosylation reaction.[5] In our attempts to synthesize a dihydrothiopyrano-nucleoside, the thioglycosylation step is a key factor in obtaining the desired nucleoside, because the reaction can occur at either the α- or the γ-position of the dihydrothiopyran sulfoxide **7** (Scheme 1).



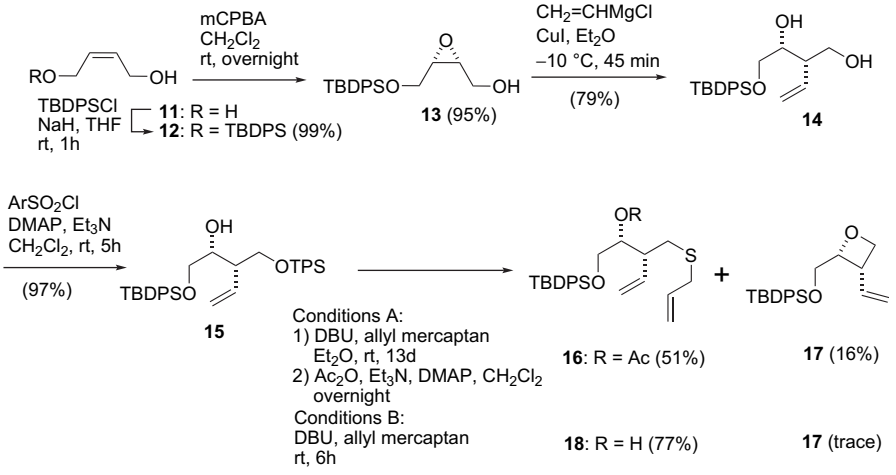
Scheme 1. The Pummerer-type thioglycosylation reaction using dihydrothiopyran sulfoxide.

It is difficult to predict the regioselectivity of this vinylogous Pummerer-type reaction.[6] It is noteworthy, however, that we successfully synthesized 4′-thio-2′-methylene-nucleosides **5**, which was produced in a Pummerer-type thioglycosylation reaction of the corresponding 2-methylene-4-thiosugar sulfoxide and silylated uracils.[2a,g] This result encouraged us to pursue the synthesis of dihydrothiopyrano-nucleoside using the Pummerer-type reaction strategy. We herein report on the synthesis of dihydrothiopyran sulfoxide and its conversion to the dihydrothiopyrano-nucleoside **6** by a Pummerer-type thioglycosylation reaction.[3] Some of the factors that influence the regioselectivity of the reaction are also discussed.

2. Results and discussion

To prepare the thiosugar portion of the molecule, it was necessary to synthesize a 5-subsutituted dihydrothiopyran skeleton. Among the several reports describing the synthesis of dihydrothiopyran, the method involving the use of ring closing metathesis (RCM) appeared to be the most promising approach. Our strategy was to synthesize an allyl butenyl sulfide derivative, and an RCM reaction was attempted. The known monosilylated allyl alcohol **12** was obtained from 2-butene-1,4-diol **11** in 99% yield.[7a,c] The enantiomerically pure epoxy alcohol **13** can be prepared using the Sharpless asymmetric epoxidation, as has previously been described.[7b,c] However, we were interested in obtaining the target compound as a racemic mixture, because the antiviral evaluation of the racemic target compounds would provide data regarding both enantiomers in a single procedure. Thus, we prepared a racemic mixture of **13** and treated the allyl alcohol **12** with *m*-CPBA in CH_2Cl_2 to give **13** in 95% yield. The epoxide ring of **13** was cleaved by a known method with minor modifications to give the vinyl diol **14** regioselectively.[7b,c,8] Selective monotosylation at the primary hydroxyl group of **14**, however, was unsuccessful. The typical reaction for tosylation (TsCl, Et_3N, DMAP, CH_2Cl_2) resulted in the predominant formation of the ditosylated derivative (data not shown). This problem was overcome by using a more bulky 2,4,6-triisopropylbenzenesulfonyl (TPS) group, instead of a tosyl group. The reaction of **14** with TPSCl, triethylamine, and DMAP in CH_2Cl_2 gave the desired mono-TPS derivative **15** in 97% yield. The formation of the di-TPS derivative could be suppressed by appropriately adjusting the reaction conditions. A nucleophilic substitution reaction of **15** with allyl mercaptan and DBU in Et_2O gave allyl butenyl sulfide **16** and an oxetane derivative **17** in 51 and 16% yields, respectively, after acetylation (condition A). This result suggests that intramolecular oxetane formation competed with the introduction of the ally sulfide moiety. The formation of the undesired oxetane **17** was successfully suppressed when the substitution reaction was performed using allyl mercaptan as the solvent. The allyl sulfide **18** was obtained in 77% yield with only trace amounts of the oxetane derivative **17** (conditions B). An attempt to convert the oxetane derivative **17** to **18** by treatment with allyl mercaptan and DBU was not successful. This result suggests that the substitution of the TPS group occurs via a direct S_N2 reaction (Scheme 2) and that oxetane **17** was not involved to the formation of the allyl sulfide.

In order to construct a dihydrothiopyran skeleton, an RCM reaction of **18**, as described above, was attempted. After acetylation of the hydroxyl group, the RCM reaction of **16** with the first Grubbs catalyst was attempted. However, the reaction was sluggish and the starting **16** was recovered in 83%. When the same reaction was performed in refluxing benzene, dihydrothiopyran **19** was obtained in 20% yield with 57% of **16** being recovered. In contrast to these results, the use of the second Grubbs catalyst in refluxing benzene

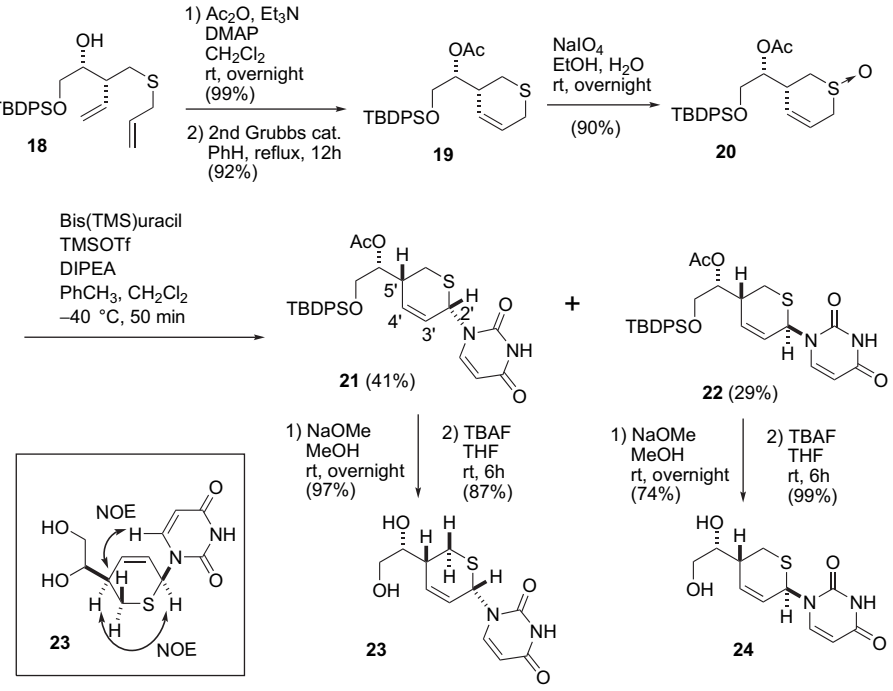


Scheme 2. Synthesis of an allyl butenyl sulfide derivative **18**.

greatly improved the reaction and gave **19** in 92% yield.[9] Upon treatment with $NaIO_4$ in EtOH/H_2O overnight, compound **19** was oxidized to give a diastereomeric mixture of a sulphoxide derivative **20** in 90% yield. Following our initial plan, the sulfoxide **20** was subjected to the Pummerer-type thioglycosylation reaction. The conditions optimized for the synthesis of 4′-thiouridine were applied to the reaction of **20**.[4] Treatment of the sulphoxide **20** with bis(trimethylsilyl)uracil, TMSOTf, and DIPEA in toluene and CH_2Cl_2 (1:1, v/v) at −40 °C gave the dihydrothiopyranyluracil derivatives **21** and **22** in 41 and 29% yields, respectively. Adducts produced by reaction at the 4′-position were not observed. The stereochemistry of the dihydrothiopyranyluracil derivative **21** was elucidated by NOE experiments of **23**, which was obtained by deprotection with sodium methoxide and subsequent treatment with TBAF. The final product was determined to be the cis-isomer. On the other hand, the deprotection procedure was applied to **22** giving dihydrothiopyranyluracil **24**, the structure of which was determined by X-ray crystallographic analysis (Scheme 3).[3]

above. Treatment of **30** with TBAF gave the ring-expanded 4′-thio-D4U **6** in 80% yield. NOE experiments of **6** revealed that the major product of the Pummerer-type thioglycosylation had a cis-stereochemistry. Similarly, deprotection of **31** gave the trans-isomer **32** in excellent yield. It is noteworthy that the Pummerer-type thioglycosylation of **29** as well as of **20** both gave cis-isomers as major products. However, the reason for the predominant formation of these cis-isomers is currently unclear (Scheme 4).

As a final target, we selected a dihydrothiopyrano-uridine derivative, which contains a hydroxyl group in place of a hydroxymethyl group at the 5′-position. The target itself has a unique structure and has potential biological activity. In addition, it would be expected to serve as an important synthetic intermediate in the preparation of novel nucleoside analogues including phosphonomethyl derivatives.[11] The synthesis of the compound is also of interest in terms of the influence of substituent group at the 5′-position on the regioselectivity of the Pummerer-type thioglycosylation reaction.



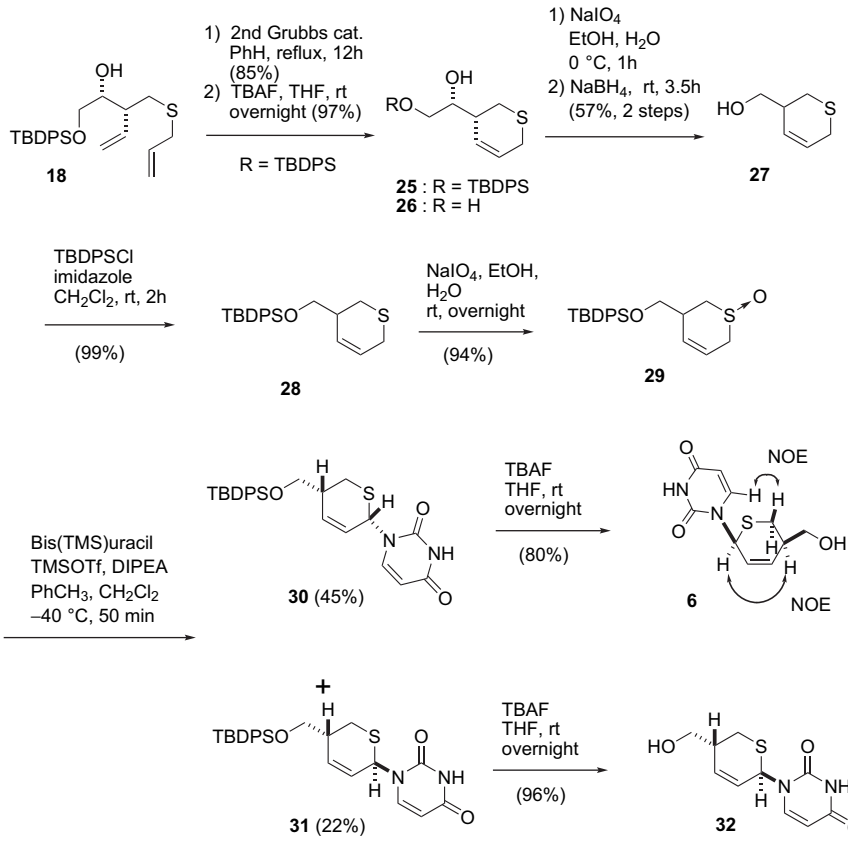
Scheme 3. Synthesis of dihydrothiopyrano-uridine derivatives **23** and **24**.

Our next target was the dihydrothiopyrano-uridine **6**, a ring-expanded *apio*-nucleoside[10] analogue of 4′-thio-D4-uridine. As in the case described above, the RCM-reaction of **18**, without protection of the secondary hydroxyl group, using the second Grubbs catalyst resulted in the formation of the dihydrothiopyran derivative **25** in 85% yield. After deprotection of the TBDPS group, oxidative scission of the *cis*-diol by treating **26** with $NaIO_4$ followed by sodium borohydride treatment gave 3-hydroxymethyl-3,6-dihydrothiopyran **27** in 57% yield. The selective diol cleavage of **26** was possible, since the cleavage reaction was faster than the oxidation of the sulfide to the sulfoxide. As expected, the oxidation to sulfoxide **29**, after protection of the primary hydroxyl group with a TBDPS group, was carried out by treatment with $NaIO_4$ and the reaction gave **29** in good yield. Using the same conditions described above, the Pummerer-type thioglycosylation reaction of **29** with bis(trimethylsilyl)uracil gave the desired ring-expanded 4′-thio-*apio*-uridine derivatives **30** and **31** in 45 and 22% yields, respectively. No γ-adducts were detected, as in the case described

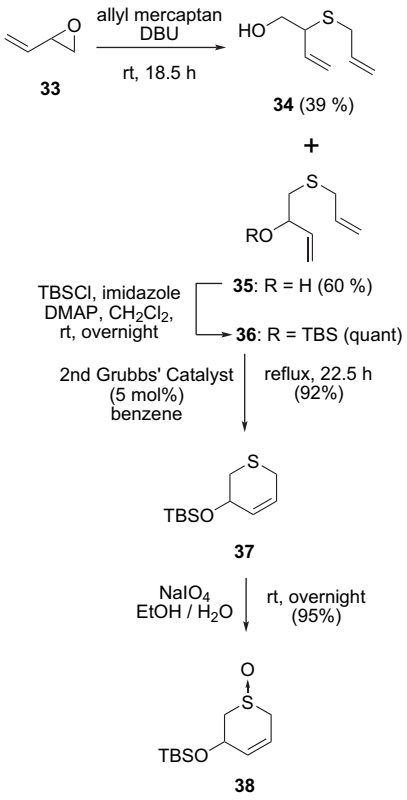
The dihydrothiopyran **37**, a precursor of the substrate of the Pummerer-type thioglycosylation, was synthesized following a previously reported method.[9] Commercially available butadiene monoxide **33** was treated with allyl mercaptan in the presence of DBU to give a mixture of **34** and **35** in 39 and 60% yields, respectively, after silica gel column separation. After protecting the secondary hydroxyl group of **35** by reaction with TBSCl, the resulting **36** was subjected to the RCM reaction catalyzed by the second Grubbs' catalyst, which gave 5-*O*-TBS-dihydrothiopyran **37** in 92% yield. The oxidation of **37**, as described above, gave the sulfoxide **38** in good yield (Scheme 5).

As in the case of sulfoxides **20** and **28**, the Pummerer-type thioglycosylation reaction of **38** was performed and the results are summarized in Table 1.

The reaction of a diastereomeric mixture of **38** (1:1) with bis(TMS)uracil in the presence of TMSOTf and diisopropylethylamine was complete within 40 min at −40 °C and gave a mixture of dihydrothiopyrano-nucleosides in a ratio of 3:3:1 (entry 1). Among

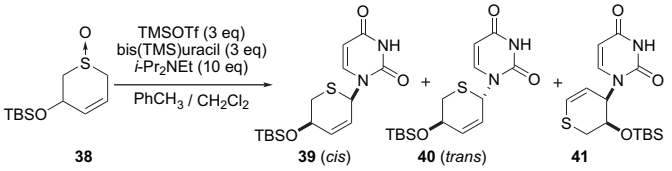


Scheme 4. Synthesis of ring-expanded 4′-thio-D4U **31**.



Scheme 5. Synthesis of 5-siloxydihydrothiopyran sulfoxide **38**.

Table 1
Summary of the Pummerer-type thioglycosylation reaction of sulfoxide **38**



Entry	38	Time/temperature	Ratio of the products			Total yield (%)
			39	40	41	
1	Mixture	40 min/−40 °C	3	3	1	62
2	Less polar	1.5 h/−40 °C	3.6	3.6	1	68
3		16 h/−40 °C→5 h/rt	0	0	1	53
4	More polar	10 min/−40 °C	2.7	2.7	1	89
5		3 h/−40 °C	0	0	1	75

the three products obtained, the major α-adducts were isolated and their structures determined as follows. The mixture of **39**, **40**, and **41** was treated with TBAF to give a mixture of free nucleosides, from which the trans-isomer **42** was obtained in 37% by simple crystallization. The structure of **42** was confirmed by NOE experiments as shown in Chart 2. On the other hand, benzoylation of the N^3-position of the uracil ring and subsequent careful purification by silica gel column chromatography gave isomerically pure **45** in 44% yield and a mixture of **43** and **44** (56%). Compound **45** was deprotected by TBAF followed by NaOMe treatment to give the free dihydrothiopyrano-uridine derivative **46** in good yield. NOE experiments of **46**, as shown in Chart 2, clearly revealed that **45** had a cis-stereochemistry (Scheme 6).

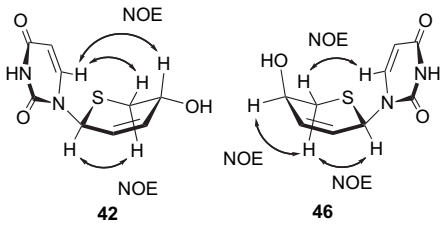
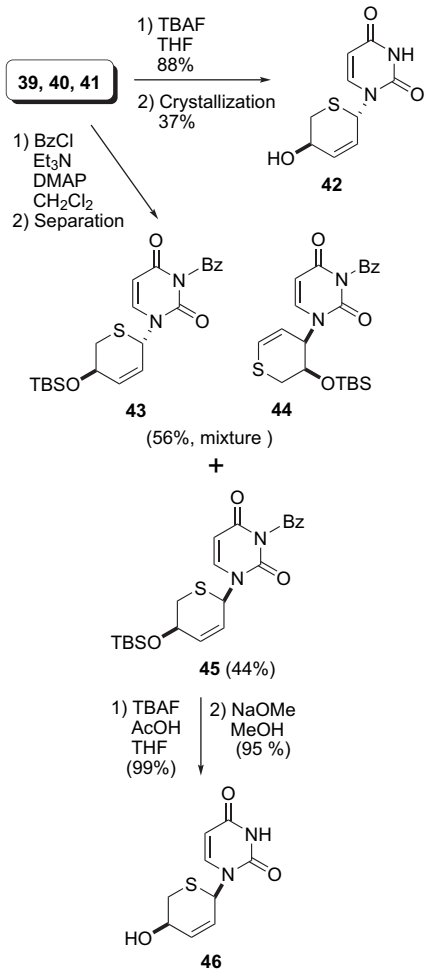


Chart 2.

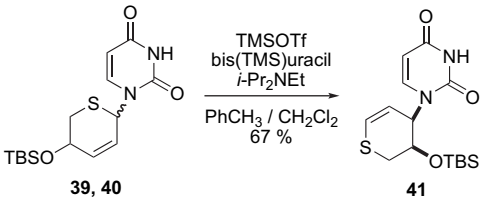


Scheme 6. Synthesis and isolation of 5-hydroxydihydrothiopyranyluracils **42** and **46**.

The most remarkable result in entry 1 is the fact that the reaction mixture contained a minor product, which presumably corresponded to a γ-adduct. This aspect of the reaction is discussed below. Another interesting aspect of the Pummerer-type thioglycosylation of **38** was whether the reaction was affected by difference of the stereochemistry of the sulfoxide.[2g,5b] We carefully separated the diastereomers by silica gel column chromatography. Thus, both of the isomers were separately subjected to the reaction, but it was not possible to determine the stereochemistries of the sulfoxides. The less polar isomer showed similar results to those obtained when a mixture was used (entry 2). The reaction of the more polar isomer, on the other hand, was complete within 10 min and gave a mixture of products in 89% yield with a similar ratio as mentioned above (entry 4). These data strongly suggest that the reaction proceeded via a common allylic sulfenium ion in both cases. The difference in the reaction velocity can be explained by the ease of formation of the allylic sulfenium ion from the more polar sulfoxide, compared to the less polar isomer. In other words, the elimination of trimethylsilanol, which occurs by way of the silylation of oxygen and the subsequent abstraction of an α-proton of the sulfoxide should proceed faster in the case of the more polar isomer than in the less polar one.[5b]

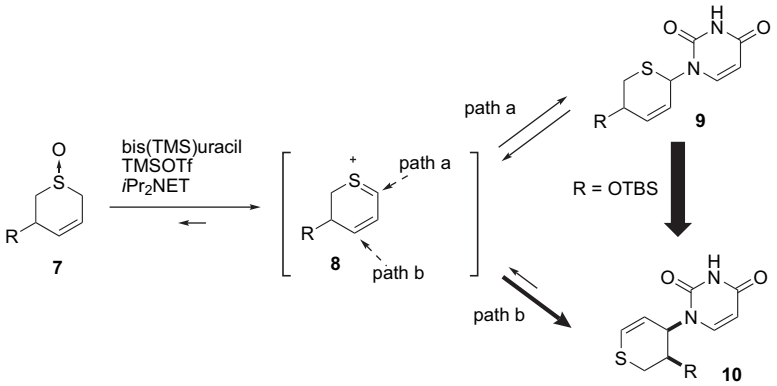
In contrast to the results for the 5-siloxymethyl derivatives **20** and **28**, the 5-siloxy derivative **38** produced the γ-adduct as a side-product (vide supra). It was interesting to find that prolonging the reaction time and increasing the reaction temperature resulted in the selective formation of the γ-adduct **41** from both of the isomeric sulfoxides (entries 3 and 5).

It is possible that the γ-adduct **41** is formed from the α-adducts **39** and **40** via regeneration of an allylic sulfenium ion. To confirm this, the products of entry 1, largely **39** and **40** were retreated under the conditions used for the Pummerer-type thioglycosylation. As expected, the starting materials were consumed and the γ-adduct **41** was isolated in 67% yield after silica gel column chromatography (Scheme 7). The relative stereochemistry of **41** was estimated as cis based on an NMR analysis (vide infra). From this result as well as those described above, the following reaction mechanism is proposed, as shown in Scheme 8.



Scheme 7. Isomerization of the α-adducts **39** and **40** to the γ-adduct **41**.

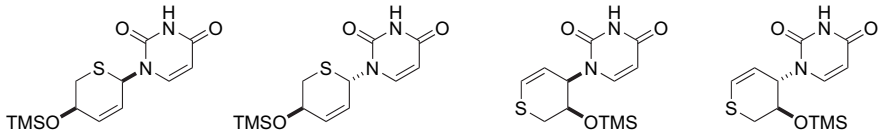
The reaction intermediate is an allylic sulfenium ion **8** generated from the reaction of sulfoxide **7**, TMSOTf, and diisopropylethylamine. An attack by the persilylated uracil at the 2-position



Scheme 8. Equilibrium between α- and γ-adducts.

of **8** (α-attack) gives rise to the α-adduct **9** (path a). It is likely that the α-attack of **8** would be the kinetically favored process, since the attack occurs at the less hindered site. However, the results suggest that an equilibrium exists between the α- and γ-adducts and that the latter should be the thermodynamically controlled product (Scheme 8). In order to obtain further support for this hypothesis, we selected 5-trimethylsiloxy derivatives **47** and **48** as simplified model compounds and their structures were estimated by theoretical calculations. Optimized conformers of every compound were surveyed by molecular mechanics (MM) calculations and were subjected to theoretical calculations by density functional theory (DFT) quantum mechanical calculations at the B3LYP/6-31G* level. The results are summarized in Table 2.

Table 2
Summary of the calculated energy of model compounds **47** and **48**. The theoretical calculations were performed by density functional theory (DFT) quantum mechanical calculations at the B3LYP/6-31G* level using SPARTAN™ (Wavefunction, Inc.). The results are shown by the relative energy to that of *cis*-**47** as a standard



cis-**47** *trans*-**47** *cis*-**48** *trans*-**48**

	cis-**47**	*trans*-**47**	*cis*-**48**	*trans*-**48**
rel. *E* (kJ/mol)	0	2.4	−19.1	−17.4

In a series of α-adducts, the trans-isomer of **47** was revealed to have a higher energy by +2.4 kJ/mol compared to that of the *cis*-**47**. It should also be noted that both of the γ-adducts were shown to have lower energies than that of *cis*-**47**: *trans*-**48** should be more stable than *cis*-**47** by 17.4 kJ/mol. The most stable product estimated by theoretical calculations was *cis*-**48**, which should be more stable than *cis*-**47** by 19.1 kJ/mol. The structure of the optimized conformer of *cis*-**48**, obtained by MM and DFT calculations, is shown in Figure 1.

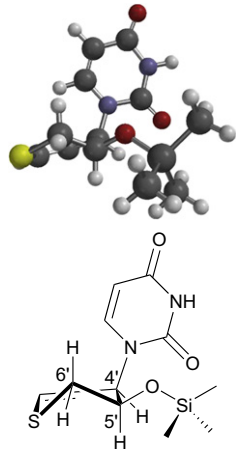


Figure 1. The structure of the optimized conformer of *cis*-**48**. (up) The 3D-structure of optimized *cis*-**48** drawn by a ball-and-stick model. (down) Schematic view of the optimized conformer of *cis*-**48**.

It can be seen that a 5′-proton of *cis*-**48** has a trans–gauche conformation related to two of the 6′-protons. This is in good agreement with the structure of **41** deduced by ^{1}H NMR data, since it was observed that the coupling constants between 5′- and 6′-protons were 9.4 and 3.1 Hz (see Experimental section). Furthermore, the fact that compound **41** has a coupling constant of 7.1 Hz corresponding to H-4′ and H-5′ is consistent with the structure of *cis*-**48** depicted in Figure 1. On the other hand, the optimized conformer of *trans*-**48** obtained by theoretical calculations indicates a gauche–gauche conformation around C5′–C6′ since both of the bulky uracil and siloxy groups occupy axial positions (data not shown). From these considerations, compound **41** obtained by isomerization of the α-adducts was determined as a cis-isomer. Therefore, there is no doubt that the cis-isomer of the γ-adduct is a thermodynamic product of the Pummerer-type thioglycosylation. However, we do not have clear explanation for the reason why the formation of any trace of *trans*-**48** was not observed despite the small energy gap between *cis*- and *trans*-**48** estimated by calculations.

Among the many reported examples of the Pummerer reaction, the reactions of α,β-unsaturated sulfoxides are known to proceed via either a vinylogous or an additive mechanism.[6] In the former reaction, the α,β-unsaturated sulfoxides bearing a γ-hydrogen generates a conjugated sulfenium ion to which a nucleophile is able to attack at either its α- or γ-position.[6] As can be seen, the vinylogous Pummerer reaction contains an issue of the regioselectivity of substitution, however, the factors that rule the selectivity of the reaction are not yet clear.[6] The reaction described above belongs to a category of the vinylogous Pummerer reaction, since the reaction intermediate is the same allylic sulfenium ion. The results point out an important feature of the reaction in which an equilibrium between α- and γ-adducts exists. This serves as a reminder that it is difficult to predict the regioselectivity of vinylogous Pummerer reactions, since the ratio of α- and γ-adducts is very likely to be influenced by the reaction conditions used. In addition, it is obvious that the substituent groups of the α,β-unsaturated sulfoxides are important: nature of the allylic sulfenium ion depends on the functional groups attached to it and this no doubt influences the equilibrium of the reaction. Indeed, our results showed that the Pummerer-type thioglycosylation of 5-alkyl substituted dihydrothiopyran sulfoxides gave only α-adducts, and that a 5-siloxy derivative gave a mixture of α- and γ-products. Another significant issue clarified in this study is that the γ-adduct appears to be a thermodynamic product. This conclusion is supported by the experimental results as well as theoretical calculations. The above findings can be useful in understanding several reported results including other dihydrothiopyran derivatives[12] and a 4-thiofuranose derivative bearing a 2-*exo*-methylene.[2a,g]

In summary, we report on the synthesis of a novel ring-expanded 4′-thio-*apio*-D4U derivative. The synthesis of 3-hydroxymethyl-3,6-dihydrothiopyran, the sugar portion of the target compound, started from 2-butene-1,4-diol and was achieved by the RCM-reaction after the introduction of vinyl and allyl sulfide moieties. The dihydrothiopyran was converted to the corresponding sulfoxide, the Pummerer-type thioglycosylation of which proceeded exclusively at the α-position and gave the desired 4′-thio-*apio*-D4U derivative. In contrast, when the same reaction was applied to the synthesis of 5-siloxydihydrothiopyrano-nucleosides, a mixture of the α- and γ-products was produced. It is interesting to note that the α-adduct

could be converted to the γ-adduct. The results suggest the existence of an equilibrium during the formation of the α- and γ-adducts and that the latter should be more thermodynamically stable than the former. This conclusion was theoretically supported by DFT calculations.

3. Experimental section

3.1. Experimental procedures and characterization data

Melting points are uncorrected. NMR spectra were recorded at 400 and 600 MHz (^{1}H), 100 and 150 MHz (^{13}C) using $CDCl_3$, CD_3OD, and DMSO-d_6 with tetramethylsilane as internal standard. Mass spectra were obtained by EI or FAB mode. Silica gel for chromatography was Fuji Silysia PSQ 100B. All the reactions described below were performed under argon atmosphere.

3.2. (*Z*)-4-(*tert*-Butyldiphenylsilanyloxy)-but-2-ene-1-ol (12)

To a suspension of NaH (800 mg, 20 mmol) in THF (40 mL) was added *cis*-2-butene-1,4-diol (1.63 mL, 20 mmol) at room temperature. After being stirred for 1 h, *tert*-butyldiphenylchlorosilane (5.14 mL, 20 mmol) was added to the mixture and the whole was stirred at room temperature for 1 h. The reaction mixture was diluted with ether and washed with 10% aq K_2CO_3 and brine. The water layer was extracted with ether and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2:1) to give **11** (6.48 g, 99%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 4.00 (t, *J*=5.6 Hz, 2H), 4.26 (d, *J*=5.8 Hz, 2H), 5.60–5.74 (m, 2H), 7.37–7.46 (m, 6H), 7.67–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.7, 58.7, 60.2, 127.7, 129.7, 130.0, 130.9, 133.4, 135.6. IR (neat, cm^{-1}): 463, 472, 491, 1642, 3435. FABMS (*m*/*z*): 327 (M^++1). HRMS calcd for $C_{20}H_{26}O_2Si$: 327.1780, found 327.1789. Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.65; H, 8.26.

3.3. ((2*R**,3*S**)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-oxiranyl)methanol (13)

To a solution of **12** (3.14 g, 9.62 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (3.90 g, 14.7 mmol) and the mixture was stirred at room temperature overnight. The reaction was quenched with satd $NaHCO_3$ and the whole was extracted with $CHCl_3$. The organic layer was washed with 10% $Na_2S_2O_3$, satd $NaHCO_3$ and brine, then dried ($MgSO_4$). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2:1) to give **13** (3.13 g, 95%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.09 (br s, 1H), 3.18–3.25 (m, 2H), 3.62 (dd, *J*=6.3, 12.3 Hz, 1H), 3.68 (dd, *J*=4.6, 12.3 Hz, 1H), 3.75 (dd, *J*=5.2, 11.8 Hz, 1H), 3.89 (dd, *J*=5.4, 11.8 Hz, 1H), 7.38–7.46 (m, 6H), 7.66–7.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.7, 56.2, 56.4, 60.7, 62.2, 127.8, 129.9, 132.8, 132.9, 135.49, 135.53. IR (neat, cm^{-1}): 454, 461, 466, 480, 612, 1427, 1645, 3434. FABMS (*m*/*z*): 343 (M^++1). HRMS calcd for $C_{20}H_{26}O_3Si$: 343.1730, found 343.1725.

3.4. (2*S**,3*R**)-4-(*tert*-Butyldiphenylsilanyloxy)-2-vinylbutane-1,3-diol (14)

To a suspension of CuI (6.66 g, 35.0 mmol) in dry ether (240 mL) was added a solution of vinylmagnesium chloride in THF (1.44 M in THF, 60.7 mL, 87.5 mmol) was added at −10 °C. After being stirred for 1 h at 0 °C, the mixture was allowed to cool to −10 °C. To this mixture was added a solution of **13** (5.99 g, 17.5 mmol) in dry ether (40 mL) and the mixture was stirred at the same temperature for 45 min. The reaction was quenched by the addition of concd NH_4OH followed by satd NH_4Cl. After the whole mixture was extracted with ether three times, the combined organic layer was washed with satd NH_4Cl and brine, then dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2:1) to give **14** (5.11 g, 79%) as a syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.33–2.36 (m, 1H), 3.62 (d, *J*=5.8 Hz, 2H), 3.67–3.75 (m, 2H), 3.89–3.93 (m, 1H), 5.09 (dd, *J*=1.9, 17.4 Hz, 1H), 5.15 (dd, *J*=1.9, 10.6 Hz, 1H), 5.82 (ddd, *J*=9.2, 10.6, 17.4 Hz, 1H), 7.35–7.44 (m, 6H), 7.62–7.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 48.3, 64.3, 66.1, 72.6, 118.8, 127.8, 129.9, 133.0, 134.6, 135.5. IR (neat, cm^{-1}): 614, 702, 740, 824, 999, 1113, 1428, 2858, 2931. FABMS (*m*/*z*): 371 (M^++1). HRMS calcd for $C_{22}H_{30}O_3Si$: 371.2043, found 371.2031.

3.5. ((1*R**,2*S**)-2-(2-(*tert*-Butyldiphenylsilanyloxy)-1-hydroxyethyl)but-3-enyl)-2,4,6-triisopropylbenzenesulfonate (15)

To a solution of **14** (1.29 g, 3.47 mmol) in CH_2Cl_2 (10 mL) were added 2,4,6-triisopropylbenzenesulfonyl chloride (2.10 g, 6.94 mmol), NEt_3 (967 μL, 6.94 mmol), and DMAP (42 mg, 0.347 mmol) and the mixture was stirred at room temperature for 5 h. The reaction was quenched with satd $NaHCO_3$. The resulting mixture was partitioned between $CHCl_3$ and brine, and the organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=9:1) to give **15** (2.14 g, 97%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.24–1.27 (m, 18H), 2.0 (s, 1H), 2.39 (d, *J*=3.9 Hz, 1H), 2.64 (d, *J*=7.7 Hz, 1H), 2.88–2.95 (m, 1H), 3.60 (d, *J*=6.8 Hz, 2H), 3.97 (d, *J*=2.9 Hz, 1H), 4.03 (dd, *J*=6.3, 9.7 Hz, 1H), 4.08–4.13 (m, 3H), 4.25 (dd, *J*=8.2, 9.7 Hz, 1H), 5.07–5.15 (m, 2H), 5.70 (dt, *J*=9.7, 17.4 Hz, 1H), 7.36–7.44 (m, 6H), 7.64 (d, *J*=6.3 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.5, 24.7, 26.8, 29.6, 34.2, 45.6, 65.9, 69.1, 70.0, 119.9, 123.7, 127.8, 129.4, 129.8, 132.4, 132.9, 135.5, 150.8, 153.7. IR (neat, cm^{-1}): 1639, 3410. FABMS (*m*/*z*): 637 (M^++1). HRMS calcd for $C_{37}H_{52}O_5SSi$: 637.3383, found 637.3401.

3.6. ((2*R**,3*R**)-3-((Allylthio)methyl)-1-(*tert*-butyldiphenylsilanyloxy)pent-4-en-2-yl)acetate (16) and (((2*R**,3*S**)-3-vinyloxetan-2-yl)methoxy)(*tert*-butyl)-diphenylsilane (17)

To a solution of **15** (410 mg, 0.624 mmol) in ether (1 mL) were added allyl mercaptan (519 μL, 6.44 mmol) and DBU (192 μL, 1.29 mmol) and the mixture was stirred at room temperature for 5 days. Ether (2 mL), allyl mercaptan (519 μL, 6.44 mmol), and DBU (192 μL, 1.29 mmol) were added and the mixture was stirred at room temperature for 8 days. The mixture was diluted with ether and washed with satd NH_4Cl, 10% $Na_2S_2O_3$, and brine. The water layer was extracted with ether and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5–10% AcOEt in *n*-hexane) to give crude **18** and **17**. A crude mixture of **18** was dissolved in CH_2Cl_2 (5 mL). To this mixture were added Et_3N (188 μL, 1.35 mmol), acetic anhydride (69 μL, 0.734 mmol), and DMAP (7.5 mg, 0.061 mmol) and the mixture was stirred at room temperature overnight. The mixture was diluted with ether and washed with satd $NaHCO_3$ and brine, then dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=20:1) to give **16** (153 mg, 51%) as a syrup.

Data for ***16***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.01 (s, 3H), 2.45 (dd, J=8.2, 13.0 Hz, 1H), 2.56 (dd, J=6.0, 13.0 Hz, 1H), 2.65–2.72 (m, 1H), 3.10 (d, J=7.2 Hz, 2H), 3.62 (dd, J=5.8, 10.2 Hz, 1H), 3.72 (dd, J=6.3, 10.2 Hz, 1H), 5.04–5.20 (m, 5H), 5.61–5.79 (m, 2H), 7.36–7.43 (m, 6H), 7.65 (d, J=7.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.0, 26.7, 32.1, 35.0, 44.3, 63.0, 74.5, 117.0, 118.5, 127.7, 129.7, 133.2, 134.3, 135.6, 135.9, 170.3. IR (neat, cm^{-1}): 702, 1113, 1233, 1638. EIMS (m/z): 468 (M^+). HRMS calcd for $C_{27}H_{36}O_3SSi$: 468.2154, found 468.2145. Anal. Calcd for $C_{27}H_{36}O_3SSi$: C, 69.19; H, 7.74. Found: C, 68.89; H, 7.76.

Crude **17** was re-chromatographed by a silica gel column (benzene) to give **17** (37 mg, 16%) as a syrup.

Data for ***17***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 2.66–2.72 (m, 1H), 3.54 (dd, J=4.8, 8.7 Hz, 1H), 3.60–3.66 (m, 2H), 4.02 (dd, J=6.8, 8.7 Hz, 1H), 4.09 (dd, J=3.4, 7.7 Hz, 1H), 4.79–4.86 (m, 2H), 5.37–5.46 (m, 1H), 7.28–7.38 (m, 6H), 7.54–7.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.9, 52.6, 71.4, 74.5, 78.6, 116.2, 127.7, 129.8, 133.6, 135.8, 136.8. IR (neat, cm^{-1}): 613, 702, 1111, 1428, 2858, 2931. EIMS (m/z): 295 (M^+-t-Bu).

3.7. (2*R**,3*R**)-3-((Allylthio)methyl)-1-(*tert*-butyldiphenylsilanyloxy)pent-4-en-2-ol (18)

To a solution of **15** (1.87 g, 2.94 mmol) in allyl mercaptan (5 mL) was slowly added DBU (878 μL, 5.88 mmol) and the mixture was stirred at room temperature for 6 h. The mixture was diluted with ether and washed with satd NH_4Cl, 10% $Na_2S_2O_3$, and brine. The water layer was extracted with ether and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **18** (960 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.33 (d, J=3.4 Hz, 1H), 2.35 (br s, 1H), 2.53 (dd, J=7.2, 12.6 Hz, 1H), 2.69 (dd, J=6.8, 12.6 Hz, 1H), 3.09 (d, J=7.2 Hz, 2H), 3.61 (d, J=6.3 Hz, 2H), 3.91–3.96 (m, 1H), 5.02–5.13 (m, 4H), 5.71–5.81 (m, 2H), 7.37–7.44 (m, 6H), 7.61–7.70 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 32.6, 35.1, 45.7, 66.2, 72.2, 117.0, 117.8, 127.8, 129.8, 133.1, 134.3, 135.5, 136.5. IR (neat, cm^{-1}): 701, 1113, 1636, 3414. EIMS (m/z): 426 (M^+). HRMS calcd for $C_{25}H_{34}O_2SSi$: 426.2049, found 426.2037.

3.8. ((*R**)-2-(*tert*-Butyldiphenylsilanyloxy)-1-((*R**)-3,6-dihydro-2*H*-thiopyran-3-yl)ethyl)acetate (19)

To a solution of **18** (289 mg, 0.677 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (207 μL, 1.49 mmol), acetic anhydride (77 μL, 0.812 mmol), and DMAP (8 mg, 0.068 mmol) and the mixture was stirred at room temperature overnight. The mixture was diluted with ether and washed with satd $NaHCO_3$ and brine, then dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=9:1) to give **16** (315 mg, 99%). Compound **16** was dissolved in dry benzene (50 mL). To this mixture was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5- dihydroimidazol-2-yl-idene][benzylidine]ruthenium(IV) dichloride (second Grubbs catalyst, 17 mg, 0.020 mmol, 3 mol%). After the mixture was kept under reflux for 4 h, second Grubbs catalyst (12 mg, 0.013 mmol, 2 mol%) was added. The mixture was kept under reflux for 8 h. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5:1) to give **19** (263 mg, 92%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.04 (s, 3H), 2.56 (dd, J=8.2, 13.0 Hz, 1H), 2.71 (dd, J=4.5, 13.0 Hz, 1H), 2.82–2.89 (m, 1H), 2.98 (d, J=17.5 Hz, 1H), 3.17 (dq, J=2.9, 17.5 Hz, 1H), 3.76 (dd, J=3.9, 11.6 Hz, 1H), 3.82 (dd, J=5.3, 11.6 Hz, 1H), 4.97–5.01 (m, 1H), 5.67 (dd, J=2.4, 11.1 Hz, 1H), 5.86–5.91 (m, 1H), 7.36–7.45 (m, 6H), 7.63–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.1, 25.2, 26.3, 26.7, 35.7, 62.9, 76.5, 125.5, 127.7, 129.8, 133.2, 135.6, 170.5. IR (neat, cm^{-1}): 702, 742, 1044, 1113, 1236, 1428, 1740, 2857, 2931. FABMS (m/z): 441 (M^++1). HRMS calcd for $C_{25}H_{32}O_3SSi$: 441.1920, found 441.1918.

3.9. (*R**)-2-(*tert*-Butyldiphenylsilanyloxy)-1-((*R**)-3,6-dihydro-1-oxy-2*H*-thiopyran-3-yl)ethyl acetate (20)

To a solution of **19** (1.00 g, 2.27 mmol) in EtOH/H_2O (1:1, 40 mL) was added $NaIO_4$ (972 mg, 4.54 mmol) at room temperature and the mixture was stirred at the same temperature overnight. The resulting insoluble materials were removed by suction. After the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:1) to give **20** (976 mg, 94%) as a mixture of diastereomers (3:2). A part of the mixture was separated by repeating silica gel column chromatography.

Data for ***20*** *(less polar)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.04 (s, 3H), 2.76 (t, J=11.1 Hz, 1H), 3.19–3.23 (m, 2H), 3.29–3.38 (m, 1H), 3.75 (dd, J=4.3, 11.6 Hz, 1H), 3.72–3.77 (m, 1H), 3.83 (dd, J=4.8, 11.1 Hz, 1H), 4.96 (dd, J=4.8, 5.8 Hz, 1H), 5.60–5.65 (m, 1H), 5.70 (d, J=10.6 Hz, 1H), 7.38–7.47 (m, 6H), 7.63–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 20.8, 26.7, 36.2, 49.4, 49.8, 62.3, 64.1, 75.0, 118.8, 127.7, 129.0, 129.9, 132.6, 135.4, 170.1. IR (neat, cm^{-1}): 1645, 2095. FABMS (m/z): 457 (M^++1). HRMS calcd for $C_{25}H_{32}O_4SSi$: 457.1869, found 457.1882.

Data for ***20*** *(more polar)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.04 (s, 3H), 2.59 (dd, J=10.6, 13.3 Hz, 1H), 3.10 (dd, J=3.9, 13.3 Hz, 1H), 3.18–3.23 (m, 1H), 3.34–3.38 (m, 2H), 3.74 (dd, J=4.3, 11.1 Hz, 1H), 3.83 (dd, J=5.8, 11.1 Hz, 1H), 5.10 (q, J=5.3 Hz, 1H), 5.65–5.68 (m, 1H), 5.83 (d, J=11.1 Hz, 1H), 7.37–7.46 (m, 6H), 7.63–7.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 20.9, 26.6, 30.1, 45.3, 46.2, 62.9, 75.0, 118.1, 127.7, 128.2, 129.8, 132.8, 135.5, 170.2. IR (neat, cm^{-1}): 1642, 2095. FABMS (m/z): 457 (M^++1). HRMS calcd for $C_{25}H_{32}O_4SSi$: 457.1869, found 457.1879.

3.10. 1-((2*R**,5*S**)-5-(1-Acetoxy-2-(*tert*-butyldiphenylsilanyloxy)-ethyl)-5,6-dihydro-2*H*-thiopyran-2-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (21) and 1-((2*S**,5*S**)-5-(1-acetoxy-2-(*tert*-butyldiphenylsilanyloxy)-ethyl)-5,6-dihydro-2*H*-thiopyran-2-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (22)

To a solution of **20** (100 mg, 0.219 mmol) in $PhCH_3/CH_2Cl_2$ (1:1, 3 mL) were added bis(trimethylsilyl)uracil (169 μL, 0.657 mmol) and *N*,*N*-diisopropylethylamine (381 μL, 2.19 mmol). After cooled to −40 °C, trimethylsilyl trifluoromethanesulfonate (129 μL, 0.657 mmol) was added and the mixture was stirred at the same temperature for 50 min. After the reaction was quenched with satd $NaHCO_3$, the resulting insoluble materials were removed by filtration. The filtrate was extracted with $CHCl_3$ three times, and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:2) to give a mixture of **21** and **22**. The mixture was separated by repeating silica gel column chromatography to give **21** (50 mg, 41%) and **22** (35 mg, 29%) as an amorphous foam.

Data for ***21***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.07 (s, 3H), 2.53 (dd, J=10.1, 14.0 Hz, 1H), 2.68 (dd, J=4.8, 14.0 Hz, 1H), 2.90–2.96 (m, 1H), 3.78 (dd, J=4.3, 11.6 Hz, 1H), 3.83 (dd, J=4.8, 11.6 Hz, 1H), 5.00–5.04 (m, 1H), 5.65 (dd, J=2.4, 8.2 Hz, 1H), 5.76 (ddd, J=2.4, 4.3, 11.1 Hz, 1H), 6.03–6.04 (m, 1H), 6.21 (d, J=11.1 Hz, 1H), 7.35 (d, J=8.2 Hz, 1H), 7.38–7.47 (m, 6H), 7.63–7.66 (m, 4H), 8.60 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.9, 23.2, 26.7, 35.8, 50.5, 62.8, 75.2, 102.6, 123.4, 127.8, 127.9, 130.0, 132.7, 135.5, 135.7, 140.7, 150.2, 163.0, 170.3. IR (KBr, cm^{-1}): 703, 1114, 1239, 1377, 1428, 1691, 1706,

1743. EIMS (*m*/*z*): 550 (M^+). HRMS calcd for $C_{29}H_{34}N_2O_5SSi$: 550.1958, found 550.1969.

Data for ***22***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.04 (s, 3H), 2.78 (dd, *J*=5.3, 14.5 Hz, 1H), 2.84 (dd, *J*=4.3, 14.5 Hz, 1H), 3.02 (br s, 1H), 3.77 (dd, *J*=3.9, 12.1 Hz, 1H), 3.82 (dd, *J*=5.3, 12.1 Hz, 1H), 5.11 (dt, *J*=4.3, 7.7 Hz, 1H), 5.74–5.78 (m, 2H), 6.11–6.12 (m, 1H), 6.20 (dq, *J*=2.2, 11.1 Hz, 1H), 7.37–7.46 (m, 7H), 7.63–7.65 (m, 4H), 8.87 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 20.9, 24.7, 26.7, 33.6, 50.5, 62.8, 75.3, 102.9, 124.5, 127.7, 129.8, 132.7, 134.8, 135.4, 140.8, 150.3, 163.4, 170.1. IR (neat, cm^{-1}): 506, 703, 759, 1113, 1235, 1375, 1694. EIMS (*m*/*z*): 551 (M^++1). HRMS calcd for $C_{29}H_{34}N_2O_5SSi$: 550.1958, found 550.1976.

3.11. 1-((2*S**,5*R**)-5,6-Dihydro-5-(1,2-dihydroxyethyl)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (23)

To a solution of **21** (346 mg, 0.628 mmol) in MeOH (10 mL) was added a solution of NaOMe (108 mg in 2 mL of MeOH) and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of dry ice and the solvents were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O and the separated organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was passed through a short silica gel column (*n*-hexane/ethyl acetate=1:2) to give a deacetylated product (309 mg, 97%). The deacetylated product was dissolved in THF (10 mL). To this mixture was added TBAF (1 M THF solution, 0.310 mL, 0.310 mmol) and the mixture was stirred at room temperature for 6 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=4:1) to give **23** (142 mg, 87%). Analytically pure **23** was obtained by crystallization from MeOH. Mp 146–148 °C. UV (MeOH): λ_{max} 205, 268 nm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45 (overlapped with DMSO, 1H), 2.58 (dd, *J*=5.3, 13.5 Hz, 1H), 2.65 (dd, *J*=11.6, 13.5 Hz, 1H), 3.41–3.51 (m, 3H), 4.64–4.67 (m, 1H), 4.90 (d, *J*=4.8 Hz, 1H), 5.59 (d, *J*=7.7 Hz, 1H), 5.77–5.83 (m, 2H), 6.36–6.41 (m, 1H), 7.62 (d, *J*=7.7 Hz, 1H), 11.42 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.0, 38.0, 49.6, 63.0, 72.9, 101.5, 122.1, 136.9, 141.5, 150.2, 163.1. IR (KBr, cm^{-1}): 1215, 1384, 1468, 1667, 1701, 2931, 3203, 3346. EIMS (*m*/*z*): 270 (M^+). HRMS calcd for $C_{11}H_{14}O_4N_2S$: 270.0674, found 270.0674.

3.12. 1-((2*S**,5*S**)-5,6-Dihydro-5-(1,2-dihydroxyethyl)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (24)

To a solution of **22** (59 mg, 0.107 mmol) in MeOH (5 mL) was added a solution of NaOMe (1 M in MeOH, 1 mL) and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of dry ice and the solvents were removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O and the separated organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was passed through a short silica gel column (*n*-hexane/ethyl acetate=1:2) to give a deacetylated product (34 mg, 74% conversion yield with recovering 9 mg of **22**). The deacetylated product was dissolved in THF (5 mL). To this mixture was added TBAF (1 M THF solution, 0.10 mL, 0.10 mmol) and the mixture was stirred at room temperature for 6 h. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=4:1) followed by reverse-phase ODS (Chromatorex®, Fuji silysia chemical Co) column chromatography (0–5% MeOH in H_2O) to give **24** (18 mg, 99%) as a crystal (crystallized from MeOH). Mp 206–208 °C. UV (MeOH): λ_{max} 201, 267 nm. ^{1}H NMR (400 MHz, DMSO, 50 °C) δ 2.53–2.59 (m, 1H), 2.80–2.87 (m, 2H), 3.41–3.48 (m, 2H), 3.52–3.56 (m, 1H), 4.44 (br s, 1H), 4.61 (br s, 1H), 5.61 (dd, *J*=1.9, 7.7 Hz, 1H), 5.78 (ddd, *J*=2.4, 3.9, 11.1 Hz, 1H), 5.97 (dd, *J*=2.4, 4.3 Hz, 1H), 6.34 (ddd, *J*=1.9, 4.3, 11.1 Hz, 1H), 7.53 (d, *J*=7.7 Hz, 1H), 11.28 (s, 1H). ^{13}C NMR (100 MHz, DMSO, 50 °C) δ 24.4, 36.1, 50.1, 63.6, 72.9, 102.1, 122.9, 136.9, 141.7, 150.3, 163.1. IR (KBr, cm^{-1}): 1017, 1242, 1424, 1461, 1679, 3431. EIMS (*m*/*z*): 270 (M^+). HRMS calcd for $C_{11}H_{14}O_4N_2S$: 270.0674, found 270.0674.

3.13. ((*R**)-2-(*tert*-Butyldiphenylsilanyloxy)-1-((*R**)-3,6-dihydro-2*H*-thiopyran-3-yl))ethanol (25)

To a solution of **18** (916 mg, 2.15 mmol) in dry benzene (200 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-yl-idene][benzylidine]ruthenium(IV) dichloride (second Grubbs catalyst, 55 mg, 6.44 μmol, 3 mol %). After the mixture was kept under reflux for 5 h, second Grubbs catalyst (36 mg, 4.29 μmol, 2 mol %) was added. The mixture was kept under reflux for 14 h. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=9:1) to give **25** (725 mg, 85%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 2.53 (dd, *J*=6.3, 11.6 Hz, 1H), 2.57–2.66 (m, 2H), 2.78 (d, *J*=3.9 Hz, 1H), 3.02 (d, *J*=15.9 Hz, 1H), 3.13 (dd, *J*=1.9, 15.9 Hz, 1H), 3.65–3.74 (m, 3H), 5.84 (dd, *J*=2.5, 11.0 Hz, 1H), 5.92–5.96 (m, 1H), 7.38–7.47 (m, 6H), 7.64–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.2, 26.9, 27.0, 37.0, 65.2, 74.9, 125.79, 127.8, 128.2, 129.9, 133.0, 135.5. IR (neat) cm^{-1}: 1642, 2083, 3435. FABMS (*m*/*z*): 399 (M^++1). HRMS calcd for $C_{23}H_{30}O_2SSi$: 399.1814, found 399.1821.

3.14. (*R**)-1-((*R**)-3,6-dihydro-2*H*-thiopyran-3-yl)ethane-1,2-diol (26)

To a solution of **25** (509 mg, 1.28 mmol) in THF (2 mL), was added TBAF (1 M THF solution, 1.92 mL, 1.92 mmol) and the mixture was stirred at room temperature overnight. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:2) to give **26** (199 mg, 97%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (br s, 1H), 2.64 (dd, *J*=6.8, 13.5 Hz, 1H), 2.78 (dd, *J*=4.8, 13.5 Hz, 1H), 3.07–3.17 (m, 2H), 3.63 (dd, *J*=7.2, 11.6 Hz, 1H), 3.67 (dd, *J*=3.4, 11.6 Hz, 1H), 3.73–3.77 (m, 1H), 5.85 (dt, *J*=1.93, 11.1 Hz, 1H), 5.97–6.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 27.0, 37.1, 64.3, 75.2, 126.1, 127.9. IR (neat) cm^{-1}: 1645, 2090, 3400. EIMS (*m*/*z*): 160 (M^+). HRMS calcd for $C_7H_{12}O_2S$: 160.0558, found 160.0553.

3.15. (3,6-Dihydro-2*H*-thiopyran-3-yl)methanol (27)

To a solution of **26** (30 mg, 0.187 mmol) in EtOH/H_2O (1/1, 4 mL) was added $NaIO_4$ (40 mg, 0.187 mmol). After the mixture was stirred at room temperature for 1 h, $NaBH_4$ (14 mg, 0.347 mmol) was added. The mixture was stirred at room temperature for 3.5 h. The resulting insoluble materials were removed by suction. After the filtrate was concentrated under reduced pressure, the residue was partitioned between AcOEt and 10% $Na_2S_2O_3$. The organic layer was washed with satd $NaHCO_3$ and brine, then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:1) to give **27** (14 mg, 57%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (br s, 1H), 2.47–2.55 (m, 1H), 2.71 (dd, *J*=5.8, 13.5 Hz, 1H), 2.85 (dd, *J*=4.3, 13.5 Hz, 1H), 3.03–3.09 (m, 1H), 3.12–3.18 (m, 1H), 3.66–3.71 (m, 2H), 5.69–5.74 (m, 1H), 5.96–6.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 27.1, 37.1, 65.4, 126.4, 128.4. IR (neat, cm^{-1}): 1645, 3435. EIMS (*m*/*z*): 130 (M^+). HRMS calcd for $C_6H_{10}OS$: 130.0452, found 130.0450.

3.16. ((3,6-Dihydro-2*H*-thiopyran-3-yl)methoxy)-(*tert*-butyl)diphenylsilane (28)

To a solution of **27** (71 mg, 0.545 mmol) in CH_2Cl_2 (5 mL) were added *tert*-butyldiphenylchlorosilane (210 μL, 0.818 mmol) and

imidazole (56 mg, 0.818 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with $CHCl_3$ and washed with H_2O and brine, then dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/CH_2Cl_2=1:2) to give **28** (198 mg, 99%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.57 (br s, 1H), 2.73 (dd, *J*=6.3, 13.5 Hz, 1H), 2.85 (dd, *J*=4.8, 13.5 Hz, 1H), 3.05 (s, 2H), 3.60–3.69 (m, 2H), 5.61 (d, *J*=10.6 Hz, 1H), 5.83–5.88 (m, 1H), 7.35–7.47 (m, 6H), 7.65–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.5, 26.8, 27.1, 37.7, 65.9, 125.6, 127.6, 128.7, 129.6, 133.6, 135.5. IR (neat) cm^{-1}: 701, 1112, 1428, 1642, 2858, 2931. EIMS (*m*/*z*): 368 (M^+). HRMS calcd for $C_{22}H_{28}OSSi$: 368.1630, found 368.1635.

3.17. ((3,6-Dihydro-1-oxy-2*H*-thiopyran-3-yl)methoxy)-(*tert*-butyl)diphenylsilane (29)

To a solution of **28** (246 mg, 0.67 mmol) in EtOH/H_2O (1:1, 20 mL) was added $NaIO_4$ (972 mg, 4.54 mmol) was added at room temperature and the mixture was stirred at the same temperature overnight. The resulting insoluble materials were removed by suction. After the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:1) to give **28** (241 mg, 94%) as a mixture of diastereomers (less polar/more polar=1:2). A part of the mixture was separated by repeating silica gel column chromatography.

Data for ***29*** *(less polar)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.80–2.90 (m, 2H), 3.22–3.27 (m, 1H), 3.40–3.42 (m, 1H), 3.61 (dd, *J*=6.3, 10.1 Hz, 1H), 3.70–3.78 (m, 2H), 5.60–5.69 (m, 2H), 7.38–7.47 (m, 6H), 7.63–7.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.8, 38.8, 49.6, 51.0, 66.3, 118.7, 127.8, 129.9, 130.7, 133.0, 135.5. IR (neat, cm^{-1}): 1645, 1651. EIMS (*m*/*z*): 384 (M^+). HRMS calcd for $C_{22}H_{28}O_2SSi$: 384.1579, found 384.1570.

Data for ***29*** *(more polar)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.76 (dd, *J*=8.7, 12.1 Hz, 1H), 3.05 (br s, 1H), 3.11 (dd, *J*=4.8, 13.0 Hz, 1H), 3.25 (dq, *J*=2.0, 17.0 Hz, 1H), 3.39 (d, *J*=17.0 Hz, 1H), 3.68 (dd, *J*=6.3, 9.7 Hz, 1H), 3.73 (dd, *J*=5.3, 9.7 Hz, 1H), 5.66–5.69 (m, 1H), 5.85 (dd, *J*=2.2, 10.6 Hz, 1H), 7.37–7.46 (m, 6H), 7.63–7.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 32.7, 46.2, 46.6, 66.3, 117.6, 127.7, 129.8, 130.2, 133.1, 135.5. IR (neat) cm^{-1}: 702, 1040, 1112, 1428, 1651, 2857. EIMS (*m*/*z*): 385 (M^++1). HRMS calcd for $C_{22}H_{28}O_2SSi$: 384.1579, found 384.1563.

3.18. 1-((2*S**,5*R**)-5-(*tert*-Butyldiphenylsilanyloxymethyl-5,6-dihydro)-2*H*-thiopyran-2-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (30), and 1-((2*R**,5*R**)-5-(*tert*-butyldiphenylsilanyloxymethyl-5,6-dihydro)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (31)

To a solution of **29** (2.37 g, 0.616 mmol) in $PhCH_3/CH_2Cl_2$ (1:1, 30 mL) were added bis(trimethylsilyl)uracil (475 μL, 1.85 mmol) and *N*,*N*-diisopropylethylamine (1.07 mL, 6.16 mmol). After cooled to −40 °C, trimethylsilyl trifluoromethanesulfonate (3649 μL, 1.85 mmol) was added and the mixture was stirred at the same temperature for 50 min. After the reaction was quenched with satd $NaHCO_3$, the resulting insoluble materials were removed by filtration. The filtrate was extracted with $CHCl_3$ three times, and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=1:1) to give **30** (137 mg, 46%) and **31** (64 mg, 22%) as amorphous foam.

Data for ***30***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.62 (m, 1H), 2.68 (dd, *J*=4.8, 13.5 Hz, 1H), 2.74 (dd, *J*=10.6, 13.5 Hz, 1H), 3.75 (d, *J*=4.3 Hz, 2H), 5.60 (dd, *J*=1.9, 8.2 Hz, 1H), 5.78 (dd, *J*=2.4, 11.1 Hz, 1H), 6.01–6.02 (m, 1H), 6.20 (d, *J*=11.1 Hz, 1H), 7.41–7.46 (m, 7H), 7.57–7.64 (m, 4H), 9.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.4, 26.8, 37.8, 50.4, 66.2, 102.5, 123.2, 127.7, 129.9, 132.9, 135.5, 137.6, 140.9, 150.4, 163.4. IR (neat, cm^{-1}): 702, 741, 1112, 1239, 1378, 1428, 1460, 1682, 3422. EIMS (*m*/*z*): 478 (M^+). HRMS calcd for $C_{26}H_{30}N_2O_3SSi$: 478.1746, found 478.1759.

Data for ***31***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.69 (br s, 1H), 2.85 (dd, *J*=3.9, 14.0 Hz, 1H), 2.94 (dd, *J*=3.9, 14.0 Hz, 1H), 3.66 (dd, *J*=5.3, 10.1 Hz, 1H), 3.75 (dd, *J*=8.7, 10.1 Hz, 1H), 5.72–5.76 (m, 2H), 5.96–5.97 (m, 1H), 6.13 (ddd, *J*=1.9, 4.8, 10.6 Hz, 1H), 7.38–7.47 (m, 7H), 7.63–7.66 (m, 4H), 9.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 23.9, 26.8, 36.2, 50.4, 63.3, 102.7, 124.1, 127.8, 129.8, 133.1, 133.3, 135.5, 140.9, 150.2, 163.1. IR (neat, cm^{-1}): 703, 740, 1111, 1238, 1378, 1427, 1461, 1645, 3434. EIMS (*m*/*z*): 478 (M^+). HRMS calcd for $C_{26}H_{30}N_2O_3SSi$: 478.1746, found 478.1736.

3.19. 1-((2*S**,5*R**)-5,6-Dihydro-5-(hydroxymethyl)-2*H*-thiopyran-2-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (6)

To a solution of **30** (137 mg, 0.286 mmol) in THF (20 mL) was added TBAF (1 M THF solution, 429 μL, 0.429 mmol) and the mixture was stirred at room temperature overnight. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/EtOH=9:1) to give **6** (55 mg, 80%) as a crystal (crystallized from MeOH). Mp 157–159 °C. UV (MeOH): λ_{max} 205, 267 nm. ^{1}H NMR (400 MHz, CD_3OD, 35 °C) δ 2.38–2.46 (m, 1H), 2.55 (dd, *J*=10.1, 13.5 Hz, 1H), 2.63 (dd, *J*=5.3, 13.5 Hz, 1H), 3.56 (d, *J*=5.8 Hz, 2H), 5.59 (d, *J*=8.2 Hz, 1H), 5.75 (ddd, *J*=2.4, 4.8, 10.6 Hz, 1H), 5.84–5.86 (m, 1H), 6.18 (d, *J*=10.6 Hz, 1H), 7.62 (d, *J*=8.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 24.2, 39.6, 51.9, 65.5, 102.7, 124.3, 138.5, 143.4, 152.1, 166.1. IR (KBr, cm^{-1}): 559, 1098, 1241, 1353, 1384, 1462, 1616, 1699, 3034. EIMS (*m*/*z*): 240 (M^+). HRMS calcd for $C_{10}H_{12}N_2O_3S$: 240.0569, found 240.056. Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 50.27; H, 5.00; N, 11.44.

3.20. 1-((2*R**,5*R**)-5,6-Dihydro-5-(hydroxymethyl)-2*H*-thiopyran-2-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (32)

By the same procedure described above, compound **32** (31 mg, 96%) was obtained from **31** (64 mg, 0.134 mmol). Mp 183–184 °C. UV (MeOH): λ_{max} 268 nm. ^{1}H NMR (400 MHz, CD_3OD) δ 2.60–2.62 (m, 1H), 2.83 (dd, *J*=2.9, 14.0 Hz, 1H), 2.96 (dd, *J*=3.9, 14.0 Hz, 1H), 3.59 (dd, *J*=4.8, 10.6 Hz, 1H), 3.66 (dd, *J*=9.1, 10.6 Hz, 1H), 5.68 (d, *J*=7.7 Hz, 1H), 5.83–5.89 (m, 2H), 6.27 (dd, *J*=5.3, 9.7 Hz, 1H), 7.70 (d, *J*=7.7 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 23.8, 37.3, 51.6, 62.5, 102.9, 124.7, 136.9, 143.4, 152.1, 166.1 IR (KBr) cm^{-1}: 1047, 1236, 1351, 1386, 1419, 1452, 1699, 3316. EIMS (*m*/*z*): 240 (M^+). HRMS calcd for $C_{10}H_{12}N_2O_3S$: 240.0569, found 240.0564. Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 50.47; H, 5.14; N, 11.32.

3.21. 1-Allylthio-2-(*tert*-butyldimethylsilyloxy)-3-butene (36)

To a solution of **35**[9] (3.64 g, 25.2 mmol) in CH_2Cl_2 (100 mL) were added imidazole (2.58 g, 37.8 mmol), DMAP (612 mg, 5.05 mmol), and *tert*-butyl-dimethylchlorosilane (5.70 g, 37.8 mmol). After being stirred at room temperature overnight, the mixture was diluted with CH_2Cl_2. The diluted mixture was washed with satd NaCl and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=5:1) to give **36** (6.52 g, quant) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 2.47 (dd, *J*=6.3, 13.0 Hz, 1H), 2.55 (dd, *J*=6.3, 13.0 Hz, 1H), 3.10 (d, *J*=6.8 Hz, 2H), 4.17 (dd, *J*=6.3, 12.6 Hz, 1H), 5.02–5.07 (m, 3H), 5.17 (d, *J*=16.9 Hz, 1H), 5.68–5.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.73, −4.47, 18.2, 25.9, 35.6, 38.3,

73.7, 115.0, 117.0, 134.6, 140.2. IR (neat, cm^{-1}): 777, 837, 1256, 2930. EIMS (*m*/*z*): 258 (M^+). HRMS calcd for $C_{13}H_{26}OSSi$: 258.1474, found 258.1485.

3.22. 3-(*tert*-Butyldimethylsilyloxy)-6*H*-dihydrothiopyran (37)

To a solution of **36** (653 mg, 2.53 mmol) in dry benzene (150 mL) was added tricyclohexylphosphine-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-yl-idene][benzylidine]ruthenium(IV) dichloride (second Grubbs catalyst, 55 mg, 6.44 μmol, 3 mol %). After the mixture was kept under reflux for 5 h, second Grubbs catalyst (99 mg, 0.12 mmol, 3 mol %) was added. The mixture was kept under reflux for 9.5 h. Another 68 mg (0.08 mmol, 2 mol %) of second Grubbs catalyst was added. The mixture was kept under reflux for 13 h. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=99.9:0.1) to give **37** (537 mg, 92%) as a syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.80 (s, 9H), 2.50–2.60 (m, 2H), 2.69 (d, *J*=2.3, 17.7 Hz, 1H), 3.17 (dd, *J*=2.3, 17.7 Hz, 1H), 4.29–4.33 (m, 1H), 5.58 (d, *J*=11.6 Hz, 1H), 5.70–5.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.75, −4.56, 18.1, 24.6, 25.8, 31.6, 65.8, 125.0, 133.3. IR (neat) cm^{-1}: 776, 836, 871, 1074, 1256, 2857, 2929, 2956. EIMS (*m*/*z*): 230 (M^+). HRMS calcd for $C_{11}H_{22}OSSi$: 230.1161, found 230.1180.

3.23. 3-(*tert*-Butyldimethylsilyloxy)-6*H*-dihydrothiopyran-1-oxide (38)

To a solution of **37** (1.21 g, 5.23 mmol) in EtOH/H_2O (1:1, 15 mL) was added $NaIO_4$ (1.23 g, 5.75 mmol) was added at room temperature and the mixture was stirred at the same temperature overnight. The resulting insoluble materials were removed by suction. After the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=97:3) to give **38** (1.20 g, 95%) as a mixture of diastereomers (less polar/more polar=1:2). A part of the mixture was separated by repeating silica gel column chromatography.

Data for ***38*** *(less polar)*: ^1H NMR (600 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.91 (s, 9H), 2.97 (t, *J*=10.6 Hz, 1H), 3.30 (dq, *J*=2.9, 12.5 Hz, 1H), 3.51 (dddd, *J*=1.5, 3.3, 5.9, 12.5 Hz, 1H), 3.73 (ddt, *J*=3.7, 7.0, 10.6 Hz, 1H), 4.57–4.61 (m, 1H), 5.63 (ddt, *J*=1.8, 7.0, 10.6 Hz, 1H), 5.77 (dt, *J*=2.6, 10.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.8, −4.6, 18.1, 25.7, 49.2, 56.2, 65.3, 117.4, 134.1. IR (neat, cm^{-1}): 776, 838, 1007, 1081, 1259, 1474, 2858, 2954. EIMS (*m*/*z*): 247 (M^++1). Anal. Calcd for $C_{11}H_{22}O_2SSi$: C, 53.61; H, 9.00. Found: C, 53.50; H, 9.11.

Data for ***38*** *(more polar)*: ^1H NMR (600 MHz, $CDCl_3$) δ 0.12 (d, *J*=2.93 Hz, 6H), 0.91 (s, 9H), 2.85 (ddd, *J*=1.5, 7.3, 12.8 Hz, 1H), 3.15–3.31 (m, 2H), 3.55 (ddd, *J*=1.5, 4.8, 13.5 Hz, 1H), 4.80 (dddd, *J*=1.46, 5.9, 7.3, 11.7 Hz, 1H), 5.65 (ddt, *J*=1.5, 3.7, 10.6 Hz, 1H), 5.92 (dddd, *J*=2.2, 4.8, 5.9, 10.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.74, −4.66, 18.1, 25.7, 47.0, 52.1, 62.9, 117.7, 132.9. IR (neat, cm^{-1}): 471, 475, 492, 778, 837, 1042, 1078, 1254, 2929. EIMS (*m*/*z*): 246 (M^+). Anal. Calcd for $C_{11}H_{22}O_2SSi$: C, 53.61; H, 9.00. Found: C, 53.24; H, 9.00.

3.24. 1-((2*R**,5*R**)-5,6-Dihydro-5-(*tert*-butyldimethylsilyloxy)-2*H*-thiopyran-2-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (39 (cis)), 1-((2*R**,5*S**)-5,6-dihydro-5-(*tert*-butyldimethylsilyloxy)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (40 (trans)) (Table 1, entry 4)

To a solution of **38** (less polar, 50 mg, 0.20 mmol) in $PhCH_3$/CH_2Cl_2 (1:1, 2 mL) were added bis(trimethylsilyl)uracil (156 μL, 0.61 mmol) and *N*,*N*-diisopropylethylamine (353 μL, 2.03 mmol). After cooled to −40 °C, trimethylsilyl trifluoromethanesulfonate (120 μL, 0.61 mmol) was added and the mixture was stirred at the same temperature for 10 min. After the reaction was quenched with satd $NaHCO_3$, the resulting insoluble materials were removed by filtration. The filtrate was extracted with $CHCl_3$ three times, and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=3:2) to give a mixture of **39**, **40,** and **41** (61 mg, 89%) as an amorphous foam.

3.25. 1-((3*S**,4*R**)-3-(*tert*-Butyldimethylsilyloxy)-3,4-dihydro-2*H*-thiopyran-4-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (41)

By the same procedure described above, a mixture of **39**, **40**, and **41** (63.5 mg, 0.186 mmol) was retreated. Then, the mixture was stirred at room temperature for 10 days. After the reaction was quenched with satd $NaHCO_3$, the resulting insoluble materials were removed by filtration. The filtrate was extracted with $CHCl_3$ three times, and the combined organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=97:3) to give **41** (42.5 mg, 67%) as an amorphous foam. ^1H NMR (600 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.85 (s, 9H), 2.78 (ddd, *J*=1.3, 3.1, 12.9 Hz, 1H), 3.11 (dd, *J*=9.4, 12.9 Hz, 1H), 4.13 (ddd, *J*=3.1, 7.1, 9.4 Hz, 1H), 5.05–5.10 (m, 1H), 5.47 (dd, *J*=3.2, 10.0 Hz, 1H), 5.74 (dd, *J*=2.6, 8.1 Hz, 1H), 6.33 (dd, *J*=1.3, 2.1, 10.0 Hz, 1H), 7.20 (d, *J*=8.1 Hz, 1H), 8.07 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.06, −4.57, 17.67, 20.20, 23.48, 25.44, 25.74, 31.30, 67.89, 102.45, 117.94, 150.58, 162.53. IR (neat, cm^{-1}): 1248, 1684, 3418. EIMS (*m*/*z*): 340 (M^+). HRMS calcd for $C_{15}H_{24}N_2O_3SSi$: 340.1277, found 340.1284.

3.26. 1-((2*R**,5*S**)-5,6-Dihydro-5-hydroxy-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (42 (trans))

To a solution of **39** and **40** (852 mg, 2.5 mmol) in THF (100 mL) was added a THF solution of TBAF (1 M, 3.75 mL, 3.75 mmol). The mixture was stirred at room temperature overnight. After the solvents were removed under reduced pressure, The residue was purified by silica gel column chromatography (ethyl acetate/EtOH=10:1), then, crystallization from MeOH to give **42** (98 mg, 37%) as a crystal. Mp 199–201 °C. UV (MeOH): λ_{max} 210, 266 nm. ^1H NMR (600 MHz, CD_3OD) δ 2.81 (dd, *J*=5.9, 13.9 Hz, 1H), 3.02 (dd, *J*=3.7, 13.9 Hz, 1H), 4.34–4.37 (m, 1H), 5.69 (d, *J*=8.1 Hz, 1H), 5.84 (ddd, *J*=1.5, 4.0, 10.6 Hz, 1H), 6.11 (dd, *J*=1.8, 4.0 Hz, 1H), 6.28 (ddd, *J*=2.2, 4.0, 10.6 Hz, 1H), 7.58 (d, *J*=8.1 Hz, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 32.0, 51.9, 62.1, 103.2, 125.8, 138.3, 143.4, 152.0, 166.0. IR (KBr, cm^{-1}): 1034, 1247, 1395, 1427, 1629, 1701, 3373. EIMS (*m*/*z*): 226 (M^+). HRMS calcd for $C_9H_{10}N_2O_3S$: 226.0412, found 226.0416.

3.27. 3-Benzoyl-1-((2*R**,5*R**)-5,6-dihydro-5-(*tert*-butyldimethylsilyloxy)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (45) and 3-benzoyl-1-((2*S**,5*R**)-5,6-dihydro-5-(*tert*-butyldimethylsilyloxy)-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (43)

To a solution of **39** and **40** (348 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) were added benzoyl chloride (237 μL, 2.04 mmol), Et_3N (356 μL, 2.56 mmol), and DMAP (12 mg, 0.102 mmol). The mixture was stirred at room temperature overnight. After the reaction was quenched by adding MeOH (2 mL), the mixture was partitioned between $CHCl_3$ and H_2O. The separated organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate=2:1) to give **45** (194 mg, 44%) and **43** (containing small amount of **44**, 261 mg, 56%).

*Data for **45***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.80 (s, 9H), 2.50–2.52 (m, 2H), 4.28 (dd, J=4.4, 11.1 Hz, 1H), 5.54 (ddd, J=1.9, 3.9, 11.1 Hz, 1H), 5.71–5.74 (m, 2H), 6.07 (d, J=11.1 Hz, 1H), 7.29–7.53 (m, 4H), 7.79–7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.98, −4.95, 18.0, 25.6, 27.2, 49.8, 65.7, 102.7, 121.9, 129.1, 130.4, 131.2, 135.0, 140.5, 141.8, 149.2, 161.8, 168.4. IR (neat) cm^{-1}: 773, 1020, 1260, 1674, 1708, 1748, 2853, 2924, 2959. EIMS (m/z): 444 (M^+). Anal. Calcd for $C_{22}H_{28}N_2O_4SSi$: C, 59.43; H, 6.35; N, 6.30. Found: C, 59.38; H, 6.44; N, 6.16.

*Data for **43***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 2.84 (dd, J=4.4, 14.0 Hz, 1H), 2.96 (dd, J=8.2, 14.0 Hz, 1H), 4.51–4.54 (m, 1H), 5.71 (dd, J=2.4, 10.6 Hz, 1H), 5.88 (d, J=8.2 Hz, 1H), 6.14 (d, J=10.6 Hz, 1H), 6.36 (d, J=2.4 Hz, 1H), 7.44 (d, J=8.2 Hz, 1H), 7.49–7.53 (m, 2H), 7.64–7.68 (m, 1H), 7.93–7.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.54, −0.02, 18.1, 25.7, 33.3, 51.6, 64.0, 103.3, 124.7, 129.2, 130.5, 131.3, 135.2, 139.5, 140.7, 161.8, 168.4. IR (neat, cm^{-1}): 773, 1029, 1258, 1668, 1704, 1747, 2927. EIMS (m/z): 444 (M^+). HRMS calcd for $C_{22}H_{28}N_2O_4SSi$: 444.1539, found 444.1536.

3.28. 1-((2*R**,5*R**)-5,6-Dihydro-5-hydroxy-2*H*-thiopyran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (46)

To a solution of **45** (194 mg, 0.436 mmol) in THF (15 mL) were added acetic acid (75 μL, 1.31 mmol) and TBAF (1.09 μL, 1.09 mmol). The mixture was stirred at room temperature overnight. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc) to give desilylated product (143 mg, 99%). A part of desilylated product (43 mg, 0.130 mmol) was dissolved in dry MeOH (5 mL). To this solution was added NaOMe (27 mg, 0.5 mmol). The mixture was stirred at room temperature overnight, then neutralized by addition of dry ice. After the solvents were removed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/EtOH=8:1) to give **46** (28 mg, 95%) as a crystal. Mp 153–155 °C. UV (MeOH): λ_{max} 268 nm. ^{1}H NMR (400 MHz, CD_3OD) δ 2.65 (dd, J=9.7, 13.0 Hz, 1H), 2.73 (dd, J=5.3, 13.0 Hz, 1H), 4.30 (ddd, J=2.4, 5.3, 9.7 Hz, 1H), 5.70 (d, J=8.2 Hz, 1H), 5.76 (ddd, J=2.4, 4.3, 10.6 Hz, 1H), 5.84–5.86 (m, 1H), 6.25 (dd, J=1.4, 10.6 Hz, 1H), 7.72 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 18.4, 27.8, 51.1, 58.3, 65.6, 103.0, 124.2, 141.3, 143.2. IR (KBr, cm^{-1}): 1042, 1246, 1615, 1665, 1699. EIMS (m/z): 226 (M^+). HRMS calcd for $C_9H_{10}N_2O_3S$: 226.0412, found 226.0416.

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