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Synthesis of a novel 1,2-dithianenucleoside *via* Pummerer-like reaction, followed by Vorbruggen glycosylation between a 1,2-dithiane derivative and uracil†

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The novel 1,2-dithianenucleoside was designed as a hybrid type of modification between 4′-thioribonucleoside and altritol nucleoside. The desired compound, *i.e.*, 1-[(3*R*,4*R*,5*S*,6*R*)-4,5-dihydroxy-6-hydroxymethyl-1,2-dithianyl]uracil (20), was prepared *via* the Pummerer-like reaction, followed by Vorbruggen glycosylation between an appropriately protected 1,2-dithiane derivative and silylated uracil.

In a synthetic study of chemically-modified nucleoside units that can be applicable to nucleic acid-based therapeutics, we have reported a practical synthesis of 4′-thioribonucleosides[1] and their incorporation into oligonucleotides (ONs) to develop short-interfering RNA (siRNA) and aptamers.[2–6] Since the resulting ONs, *i.e.*, 4′-thioRNA and its analogs, showed high thermal stability in duplex formation and nuclease resistance in biological fluids,[7,8] substitution of sugar ring oxygen with a sulfur atom appears to be one of the ideal approaches to develop versatile chemically-modified ONs.

As an alternative approach to chemical modification, substitution of five-membered sugar rings into six-membered sugars or their mimics has intensely been studied by the group of Herdewijn. Thus far, hexitol, altritol, and cyclohexenyl nucleosides and their derivatives have been prepared, and incorporation of these units into ONs has been attempted. Accordingly, ONs consisting of these modified nucleoside units, *i.e.*, hexitol nucleic acid (HNA; consisting of hexitol nucleosides), altritol nucleic acid (ANA; consisting of altritol nucleosides), and cyclohexenyl nucleic acid (CeNA; consisting of cyclohexenyl nucleosides), showed high thermal stability and nuclease resistance.[9–11] In addition, HNA, ANA, and CeNA have been attempted to develop antisense and siRNA molecules due to their preferable properties as chemically-modified ONs.[12,13]

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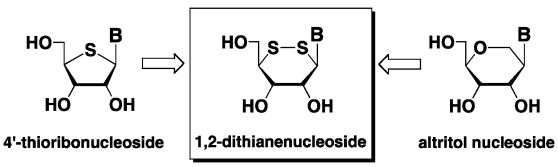
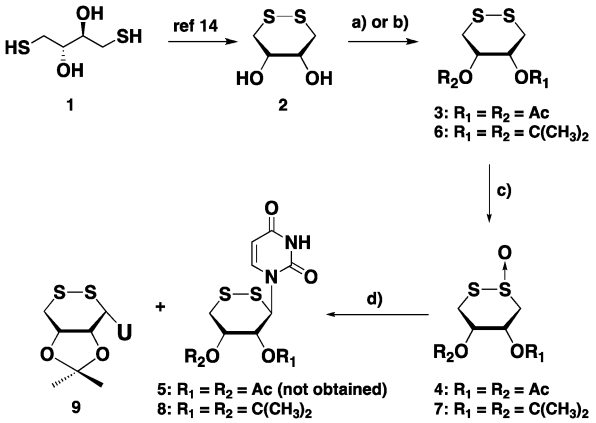


Fig. 1 Design concept of the 1,2-dithianenucleoside.

With these individual successful results in mind, we planned to develop a novel nucleoside unit, that is, 1,2-dithianenucleoside. As shown in Fig. 1, this unit has sulfur atoms and a six-membered sugar mimic, which can be considered as a hybrid type of modification, in its structure. In this communication, we report the experimental details for the synthesis of a novel 1,2-dithianenucleoside (**20**).

Thus far, we have reported a practical synthesis of 4′-thioribonucleosides *via* the Pummerer reaction between an appropriately protected sulfoxide and a silylated nucleobase.[1] Accordingly, we planned to achieve the synthesis of the desired compound using the Pummerer-like reaction of a thiolsulfinate derivative obtained from oxidation of a 1,2-dithiane derivative. To the best of our knowledge, however, no example of such a kind of reaction has been reported. Thus, we started our synthetic study using model compounds as shown in Scheme 1. Starting with 1,2-dithioerythritol (**1**), 1,2-dithiane derivative **2** was prepared according to the literature.[14] The hydroxyl groups of **2** were then protected by acetyl groups to give **3**[15] for neighboring group assistance in the subsequent Pummerer-like reaction with a nucleobase. After the requisite protection, the resulting **3** was converted into the thiolsulfinate derivative **4** (as a 7 : 1 mixture of diastereomers)[16] by *m*CPBA oxidation. In a similar manner as for the Pummerer reaction with the sulfoxide derivative,[1] a solution of the silylated uracil in a mixture of toluene–CH_2Cl_2 containing excess amount of triethylamine and trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added to a solution of **4** in CH_2Cl_2 at 0 °C. However, no coupling product with uracil was observed. Further attempts with other solvents and reaction temperatures also did not afford the desired **5**. As an alternative tactic, we changed acetyl



Scheme 1 *Reagents and conditions*: (a) Ac_2O, Et_3N, DMAP in CH_3CN; (b) 2,2-dimethoxypropane, *p*-TsOH in acetone; (c) *m*CPBA in CH_2Cl_2, −78 °C; (d) uracil, Et_3N, TMSOTf in toluene–CH_2Cl_2 or toluene–CH_3CN, 0 °C.

groups of **3** into the isopropylidene group, since this protecting group is often used in the Pummerer reaction with sulfoxide derivatives. In addition, preferable formation of the β-product is reported in spite of the absence of an acyl protecting group.[17] Thus, treatment of **2** with 2,2-dimethoxypropane in acetone in the presence of *p*-TsOH afforded **6**. Then, *m*CPBA oxidation of **6** gave thiolsulfinate derivative **7** as a 5 : 1 mixture of diastereomers.[16] To our delight, the desired Pummerer-like reaction proceeded to give the desired β-product **8** in 25% yield along with α-product **9** in 16% yield, when **7** was treated with silylated uracil in the presence of triethylamine and TMSOTf. The chemical yields of coupling products were somewhat improved to give **8** and **9** in yields of 32% and 17%, respectively, when the reaction solvent was changed to a mixture of toluene–CH_3CN. The structure of **8** was confirmed by X-ray analysis. As can be seen in Fig. 2, a uracil base is introduced at the α-position of the sulfur atom in the 1,2-dithiane skeleton. In addition, the β-configuration of glycosidic linkage is obviously proved. As mentioned above, this was the first example of introduction of a heteroatom at the α-position of the 1,2-dithiane skeleton *via* Pummerer-like reaction.

With these successful results in hand, we examined the synthesis of desired **20** (Scheme 2). Following our previous method, D-ribose was converted into the dibromide **10** in 6 steps.[18] The resulting **10** was then treated with KSAc in DMF at 100 °C to give bisthioacetate **11**. To construct the 1,2-dithiane skeleton, **11** was treated with 10% aq. KOH–MeOH (1 : 5) under O_2 atmosphere to

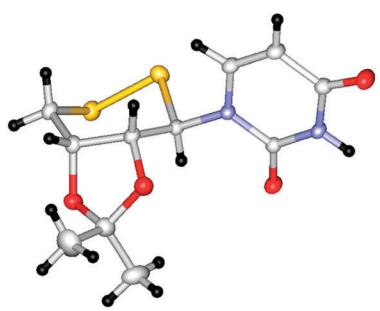
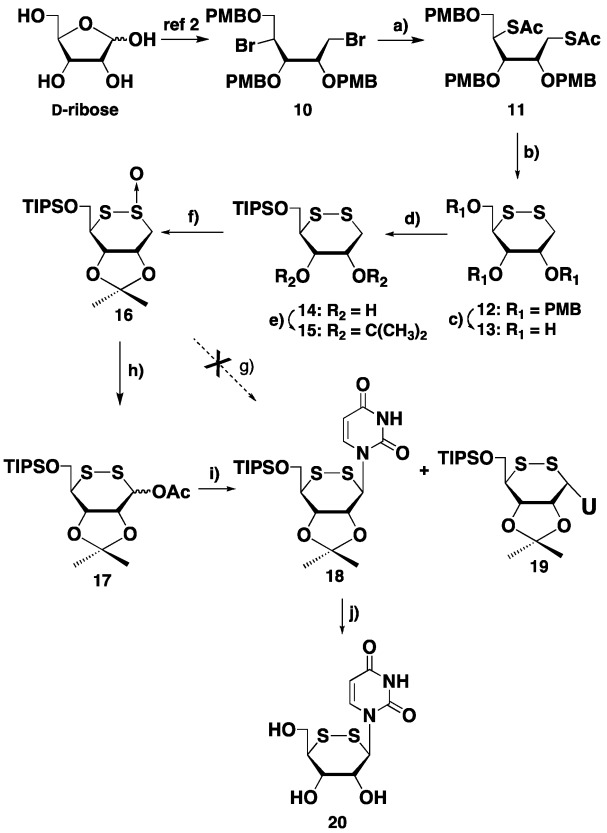


Fig. 2 X-Ray crystal structure of **8**.



Scheme 2 *Reagents and conditions*: (a) KSAc in DMF, 100 °C; (b) 10% aq. KOH–MeOH (1 : 5), O_2 atmosphere; (c) 20% TFA in CH_2Cl_2; (d) TIPSCl, imidazole in DMF; (e) 2,2-dimethoxypropane, *p*-TsOH in acetone; (f) *m*CPBA in CH_2Cl_2, −78 °C; (g) uracil, Et_3N, TMSOTf in toluene–CH_3CN, 0 °C; (h) Ac_2O, reflux; (i) uracil, *N*,*O*-bis(trimethylsilyl)acetamide, TMSOTf in CH_3CN, reflux; (j) TFA in CH_2Cl_2 (1 : 1).

give **12**. Since a model study revealed that the isopropylidene group was suitable for the *cis*-diol protection, the PMB groups of **12** were first removed by treatment with trifluoroacetic acid in CH_2Cl_2. Subsequent treatment of the resulting **13** by triisopropylsilyl chloride in DMF, followed by 2,2-dimethoxypropane afforded the fully-protected **15**. To carry out the Pummerer-like reaction, **15** was converted into thiolsulfinate derivative **16** as a 4 : 1 mixture of diastereomers by *m*CPBA oxidation.[16,19] In a similar manner as described for **8**, **16** was treated with silylated uracil in the presence of triethylamine and TMSOTf. However, no desired **18** was observed under these reaction conditions. Accordingly, **16** was converted into the acetate **17** by treatment with acetic anhydride under reflux. Although the Pummerer-like reaction was very slow and the chemical yield of **17** was rather low (19%) compared with those of the corresponding sulfoxide derivative,[1] the desired **17** was obtained by treatment with acetic anhydride. The resulting **17** was then subjected to the Vorbruggen glycosylation conditions. As a result, the β-product **18** was obtained along with the α-product **19** in yields of 37% and 15%, respectively. The β configuration of **18** and α configuration of **19** were estimated by comparison with ^{1}H-NMR spectra of **8** and **9**. Thus, H-3′ of **8**, which corresponds to the anomeric proton in natural nucleosides, appeared at 5.60 ppm in $CDCl_3$. The larger coupling constant with H-4′ ($J_{3',4'}$ = 9.8 Hz) suggested a diaxial relationship, which can be seen in the X-ray structure of **8** (Fig. 2).

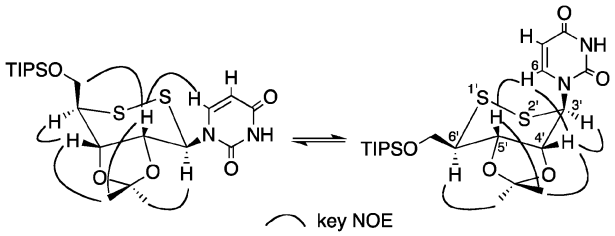


Fig. 3 Selective NOE correlations of **18**.

The H-3′ of **18** appeared at 5.78 ppm ($J_{3',4'}$ = 7.6 Hz) in $CDCl_3$, which was close to that of **8**. On the other hand, the H-3′ of **19** was observed at 6.25 ppm ($J_{3',4'}$ = 2.7 Hz), which was very close to that of **9** (6.29 ppm with $J_{3',4'}$ = 2.5 Hz). This good agreement of chemical shifts and coupling constants seems to support structures of **18** and **19**. Finally, treatment of **18** with TFA in CH_2Cl_2 afforded the desire 1,2-dithiane nucleoside **20** in 91% yield.

To confirm the structure of newly synthesized 1,2-dithianenucleoside, NOESY experiment of **18** was carried out. As can be seen in Fig. 3, the H-6 of uracil gave correlations with H-4′ and H-5′, suggesting that these protons were located on the same face. In addition, one of the acetonide methyl protons at 1.57 ppm gave correlations with H-3′ and H-6′, indicating that these protons were in α-orientation. On the other hand, the other acetonide methyl protons that appeared at 1.37 ppm were found to correlate with H-4′ and H-5′. Other correlations including H-3′/H-4′ and H-5′/H-6′ suggested that **18** was in the equilibrium with two chair conformers and all correlations strongly supported structure of **18**.

Recently, Baba *et al.* reported the synthesis of a bridged nucleoside derivative possessing disulfide linkage (disulfide-type BNA monomer).[20] The authors demonstrated that this monomer is conformationally changeable in its sugar structure using a reductant or oxidant. Since the compounds prepared in this study also have disulfide linkage, we investigated conformational changes resulting from treatment of **18** with a reductant. When **18** was treated with dithiothreitol in CH_2Cl_2 in the presence of Et_3N, formation of uracil along with a certain sugar was observed on TLC analysis. The structure of the resulting sugar was suggested as a 1,4-dithio-D-ribofuranoside derivative from ^{1}H NMR and MS spectra.[21] Unlike the disulfide-type BNA monomer, compound **20** would be utilized as a nucleoside monomer which is subject to a reductant-triggered structural change.

In conclusion, we designed the novel 1,2-dithianenucleoside possessing sulfur atoms and a six-membered sugar mimic, which can be considered a hybrid type of modification between 4′-thioribonucleoside and altritol nucleoside. The desired 1-[(3*R*,4*R*,5*S*,6*R*)-4,5-dihydroxy-6-hydroxymethyl-1,2-dithianyl]uracil (**20**) was prepared *via* the Pummerer-like reaction, followed by Vorbruggen glycosylation between an appropriately protected 1,2-dithiane derivative and silylated uracil. To the best of our knowledge, this is the first example of introduction of a heteroatom at the α-position of the 1,2-dithiane skeleton *via* Pummerer-like reaction. Accordingly, our study reported in this manuscript has novelty in not only the nucleoside derivative, but also organic chemistry. Further studies including ON synthesis containing the novel nucleoside unit(s) are in progress and will be reported elsewhere.

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