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Synthesis and Properties of 4′-ThioLNA/BNA

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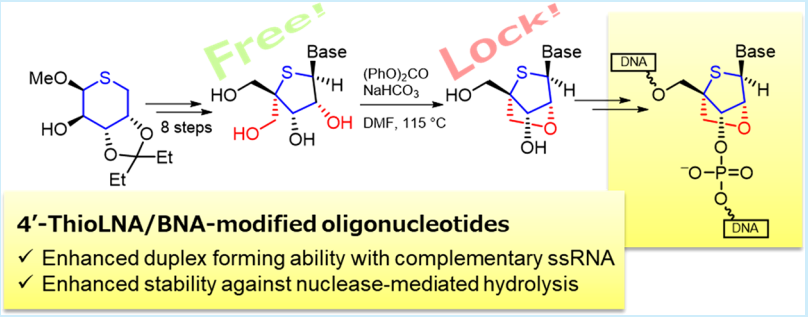

ABSTRACT: To develop a new nucleoside analogue applicable to oligonucleotide therapeutics, we designed a 4′-thio analogue of an LNA/BNA monomer. Synthesis of 4′-hydroxymethyl-4′-thioribonucleoside was achieved by a tandem ring-contraction-aldol reaction of a 5-thiopyranose derivative and the subsequent Pummerer-type thioglycosylation reaction of the corresponding sulfoxide. Treatment of 4′-hydroxymethyl-4′-thiopyrimidine nucleosides with diphenyl carbonate in the presence of catalytic $NaHCO_3$ gave the desired 4′-thioLNA/BNA monomers, which were introduced into oligonucleotides.

Oligonucleotide (ON) therapeutics, including those using antisense ONs and siRNAs, are expected to be a new modality for drug development, since they can directly suppress disease-causing mRNAs and/or miRNAs and can be obtained much more quickly than small-molecule drugs.[1] To date, 15 ON drugs have been approved and used in clinical treatment. However, general and standard strategies for ON drug development that could avoid off-target effects while still achieving sufficient nuclease resistance have not been established. A most reliable approach to the solution of this problem is to introduce a chemically modified nucleoside monomer into suitable positions of ONs in order to achieve good stability of nucleases with high affinity to the target RNA. Presently, 2′-modified nucleoside monomers bearing 2′-OMe (**1**), 2′-F (**2**), and 2′-(2-methoxy)ethoxy (MOE, **3**) substituents are used in ON drugs; however, there is still a strong demand for the development of novel nucleoside monomers suitable for ON drugs (Figure 1).[1,2]

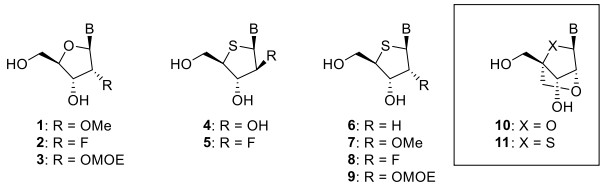

Figure 1. Structures of chemically modified nucleoside monomers.

As additional modified nucleosides, a series of 4′-thionucleosides is highly promising. We originally synthesized 2′-modified 4′-thionucleosides including 4′-thioarabinonucleosides **4**[3] and 2′-fluoro-4′-thioarabinonucleoside **5**[4] as both antiviral and antitumor agents. The latter **5** was incorporated into ONs, and the application of the resulting nucleoside to ON therapeutics was investigated by another group.[5] We also developed 2′-modified 4′-thionucleoside analogues, e.g., 2′-OMe (**7**),[6−8] 2′-F (**8**),[6] and 2′-MOE (**9**),[9] as well as 2′-deoxy (**6**),[10] and found that ONs containing these monomers are resistant to nuclease digestion and have good affinity to their respective target RNAs. To search for a novel nucleoside monomer, we focused our attention on another important class of nucleosides, the locked nucleic acid (LNA)/bridged nucleic acid (BNA) monomers (**10**).[11,12] Since the LNA/BNA also showed high affinity with RNA and nuclease resistance, its 4′-thio congener, that is, 4′-thioLNA/BNA monomer **11**, was considered to be quite a promising candidate. In this study, we report the synthesis of **11** via a tandem ring-contraction-aldol

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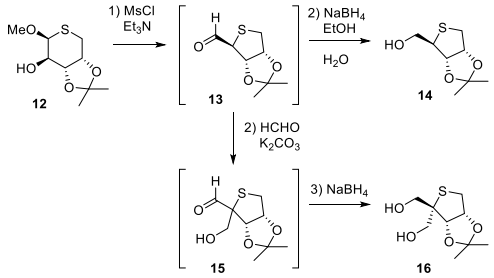
reaction and the Pummerer-type thioglycosylation and describe the properties of 4′-thioLNA/BNA.

To synthesize 4′-thioLNA/BNA monomer **11**, synthesis of 4′-hydroxymethyl-4′-thionucleoside or the corresponding 4-thioribose derivative was necessary, followed by the strategy of LNA/BNA synthesis, in which the aldol reaction of 5-aldehyde derivative with formaldehyde is typically used.[11−13] In the case of 4′-thionucleoside, Haraguchi and his co-workers reported the synthesis of various 4′-substituted 2′-deoxy-4′-thionucleosides using the aldol reaction.[14] On the other hand, we reported the synthesis of 4′-thioribonucleoside by using a tandem ring-contraction-reduction reaction of 5-thiopyranoside **12**, which gave a 4-thioribose.[15,16] In this reaction, a 5-aldehyde derivative **13** should be formed after the first ring contraction step, as shown in Scheme 1. Considering these

Scheme 1. Synthesis of 4-Hydroxymethyl-4-thioribose 16 Using the Tandem Ring-Contraction-Aldol Reaction



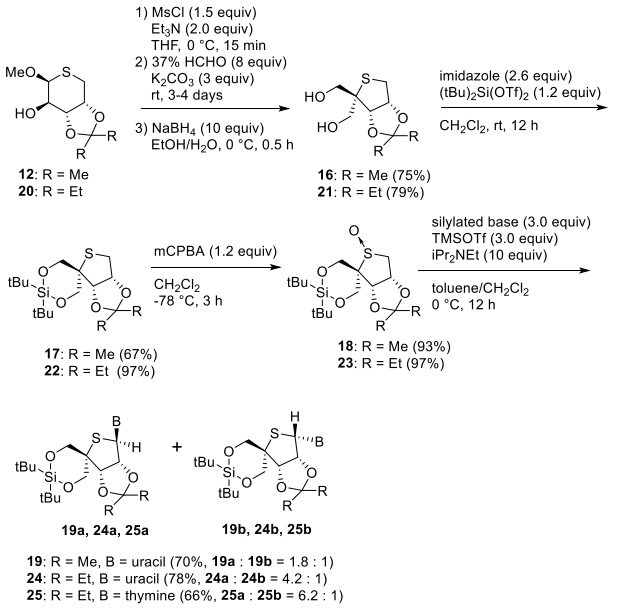
results, we intended to synthesize 4-hydroxymethyl-4-thioribose by developing a tandem ring-contraction-aldol reaction based on the above-described reaction. If we used an appropriate base catalyst, instead of $NaBH_4$, in the presence of formaldehyde, the ring contraction of 5-thiopyranoside **12** would give the 5-aldehyde **13**, which would react with formaldehyde to give an aldol product **15** in a one pot reaction. After reducing the aldehyde, the desired 4-hydroxymethyl-4-thioribose **16** was formed. Thus, we first studied the tandem reaction of **12** converting to **16** (Scheme 1).

As we expected, mesylation of **12** followed by treatment with formaldehyde in the presence of K_2CO_3 gave a mixture of the products including **15**, which were reduced by $NaBH_4$ to give **16**. However, the reaction lacked reproducibility, prompting us to search for optimized conditions for the formation of **15**. The results are summarized in Table S1 (see the Supporting Information). The reaction using less than 1 equiv of K_2CO_3 did not proceed by the aldol condensation giving **14** after hydride reduction (entry 1, Table S1 in the Supporting Information). Under the semioptimized conditions (1.5 equiv of MsCl and 3 equiv of K_2CO_3), the prolonged reaction time improved the chemical yield of **16** (entries 6−9, Table S1 in the Supporting Information). Finally, 1.5 equiv of MsCl and 8 equiv of formaldehyde in the presence of 3 equiv of K_2CO_3 in THF over 72 h were determined to be the optimized conditions for the tandem ring-contraction-aldol reaction. Under these conditions, the reaction of **12** gave **16** in 75% yield in three steps. It is noteworthy that the reaction could be handled even in multigram-scale synthesis, giving the desired product with good reproducibility. Our speculated mechanism for this reaction is also shown in Scheme S1 (see the Supporting Information).

A diol group of **16** was protected by bis(*tert*-butyl)silylene to give **17**, oxidation of which by mCPBA gave a sulfoxide **18** in good yield. As the synthesis of the sugar portion was finished, the sulfoxide **18** was subjected to the Pummerer-type thioglycosylation developed by us,[17−20] giving a mixture of anomers, **19a,b** (β/α = 1.8:1), in 70% yield. The decreased formation of β-anomer **19a**, compared with our previous results on 4′-thioribonucleosides,[15,16] strongly suggested that the shielding of the α-side by the 2,3-isopropilidene group was insufficient. In the case of 4′-thioribonucleosides, switching 2,3-isopropylidene to a 3-pentylidene group improved the β-selectivity of the Pummerer-type thioglycosylation[21] as following the Ichikawa's report regarding glycosylation of ribosyl fluoride derivatives.[22]

Thus, we repeated the synthesis of the thioglycosylation substrate from a 3-pentylidene derivative **20**, as shown in Scheme 2. All the steps including the tandem ring-contraction-

Scheme 2. Pummerer-Type Thioglycosylation of 18 and 23



aldol reaction resulted in the formation of products with good chemical yields and gave a sulfoxide derivative **23** bearing a 3-pentylidene group at the 2,3-positions. The Pummerer-type thioglycosylation of **23** afforded the desired 4′-thiouridine derivatives **24a** and **24b** in 78% yield with improved β-selectivity (β/α = 4.2:1) as expected. Also, the same reaction of **23** with silylated thymine gave a similar result (66% yield, β/α = 6.2:1).

The resulting 4′-thionucleoside derivatives **24a** and **25a**, after separation from their α-anomers by column chromatography, were desilylated by treating with NH_4F·HF in DMF to give **26** and **27**. Finally, the synthesis of 4′-hydroxymethyl-4′-thionucleosides was achieved by treatment of **26** and **27** with aqueous TFA, giving the desired uridine and ribosylthymine derivatives **28** and **29** in good yields, respectively (Scheme 3).

Next, we intended to synthesize the 4′-thioLNA/BNA monomer starting from **26**, which we had in hand. By following the method for synthesizing LNA/BNA nucleosides,[11−13] we attempted to synthesize a selectively protected compound at the 5″-hydroxyl group of **26**. However, the introduction of the tosyl and benzyl groups failed (data not shown). Only the benzoyl group could be selectively installed

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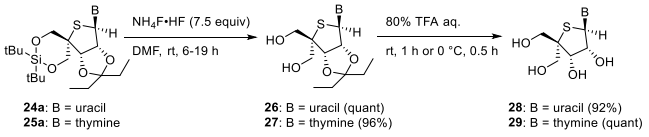
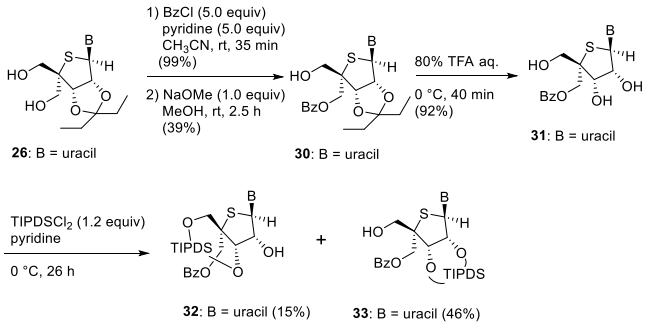
Scheme 3. Synthesis of 4′-Hydroxymethyl-4′-thiouridine (28) and 4′-Hydroxymethyl-4′-thioribosylthymine (29)



by partial deprotection of dibenzoate, giving **30** in 39% yield from **26**, as shown in Scheme 4. The structure of **30** was

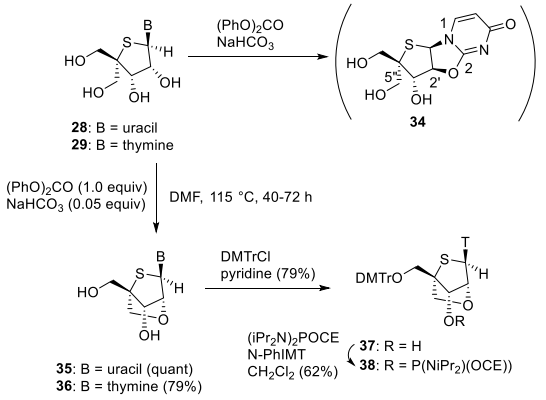
Scheme 4. Attempts to Prepare a Selectively Protected Intermediate for Synthesizing the 4′-ThioLNA/BNA Monomer



elucidated by NOE experiments (see the Supporting Information). Deprotection of the acetal group of **30** by treatment with aqueous TFA gave a 5″-O-benzoate **31** in 92% yield. In order to construct a bicyclic skeleton of the 4′-thioLNA/BNA monomer, we used the intramolecular S_N2 reaction between the 2′- and 5″-positions.[11−13] Thus, to prepare a precursor of the intramolecular S_N2 reaction, we needed to protect the 3′- and 5′-hydroxy groups of **31** selectively, and we tried to introduce a 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) group. After struggling to optimize the reaction conditions for selective protection, we found that treatment of **31** with $TIPDSCl_2$ in pyridine at 0 °C gave the desired **32** in only 15% yield along with the formation of the 2′,3′-TIPDS protected derivative **33** as a major product (Scheme 4).

From the results mentioned above, it was difficult to prepare a suitable synthetic intermediate for the intramolecular S_N2 reaction in which we allowed the attack of a 2′-alkoxide to the 5″-carbon. Alternatively, we planned to achieve the synthesis of the 4′-thioLNA/BNA monomer by using an intramolecular nucleophilic attack of 5″-alkoxide to a 2′-carbon of 2,2′-*O*-cyclo-4′-thionucleoside **34**. A similar strategy was successfully employed for the synthesis of the 2′-aminoLNA/BNA[23] and spirocyclopropyleneLNA/BNA monomers.[24] Therefore, 4′-hydroxymethyl-4′-thiouridine (**28**) was subjected to the standard conditions for 2,2′-*O*-cyclouridine synthesis,[25] as shown in Scheme 5, to give a sole product. The results of HR-MS showed that 272.0465 was a molecular ion which supported its formula as $C_{10}H_{12}N_2O_5S$ identical to **34**. However, other instrumental analyses did not support the conclusion that the structure of this ion was identical to **34**, since a broad NH signal was observed at 11.4 ppm in the ^1H NMR spectrum (see the Supporting Information). Careful comparison of ^1H NMR with that of the LNA/BNA monomer having an uracil base clearly revealed that the desired **35** was unexpectedly formed in this reaction. The reaction had good

Scheme 5. Synthesis of 4′-ThioLNA/BNA Monomers 35 and 36 and the Amidite Block 38



reproducibility so that a ribosylthymine derivative **36** was obtained in 79% yield by the successive treatment with diphenyl dicarbonate and $NaHCO_3$ in heating DMF (Scheme 5).

Although the reaction mechanism of this cyclization is not clear yet, possible reaction paths are presented in Scheme S2 (see the Supporting Information). The most plausible one is that the reaction proceeds through the formation of 2,2′-*O*-cyclonucleoside, in which the expected intramolecular nucleophilic attack of the 5″-hydroxy group has spontaneously occurred (**28** → **S6** → **34** → **35**: path A in Scheme S2). At first glance, the mechanism seems to be in line with our expectation and the experimental results, but there is a contradiction: the formation of 2,2′-*O*-cyclonucleosides, e.g. **34**, was not observed in either the **28** or **29** reactions. Another path that could reach the LNA/BNA monomer skeleton would be the 2′-hydroxy group has attacked to a 5,5″-cyclic carbonate moiety of **S5** temporally formed (**28** → **S5** → **35**: path B in Scheme S2). This also includes the problem of having the opportunity to form the bicyclo-oxetane derivative **S7**, which was not found in the reaction mixture. To clarify the reaction mechanism for the production of the LNA/BNA derivatives, further studies will first be needed to identify the true intermediate for the cyclization reaction.

To evaluate the properties of 4′-thioLNA/BNA, **36** was converted into the corresponding phosphoramidite unit **38** via **37** (Scheme 5). Then, 4′-thioLNA/BNA, **ON4** containing one 4′-thioLNA/BNA monomer in the center of the sequence, was synthesized on an automated DNA/RNA synthesizer following the standard procedure, except for a prolonged coupling time (10 min) for the incorporation of **38** into ONs (see the Supporting Information). The coupling efficiency of the phosphoramidite **38** was quantitative based on the trityl monitor (data not shown). For comparison, ONs containing LNA/BNA monomer **10** (B = thymine) and 2′-deoxy-4′-thionucleoside monomer **6** (B = thymine), **ON2** and **ON3**, were also prepared. The thermal stabilities of the synthetic ONs with complementary ssRNA and ssDNA were then evaluated by ultraviolet melting experiments in a buffer of 10 mM sodium cacodylate (pH 7.4) containing 100 mM NaCl, and the obtained melting temperatures (*T*m values) are summarized in Table 1. As is well-known, compared to the natural ON (**ON1**), the LNA/BNA-modified ON (**ON2**) forms thermally stable duplexes with ssRNA (ΔT_m = +5.8 °C) as well as ssDNA (ΔT_m = +3.8 °C), while the 2′-deoxy-4′-thiomodified ON (**ON3**) prefers ssDNA rather than ssRNA

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Table 1. T_m Values (°C) of Duplexes Formed between ONs and ssRNA or ssDNA[a]

	ssRNA		ssDNA		RNA selectivity
ONs (5′−3′)	T_m (°C)	ΔT_m (°C)	T_m (°C)	ΔT_m (°C)	T_m (RNA)− T_m (DNA) (°C)
d(gcgtttttttgct) (**ON1**)	46.2		48.4		
d(gcgttxtttgct) (**ON2**)	52.0	+5.8	52.2	+3.8	−0.2
d(gcgttytttgct) (**ON3**)	46.0	−0.2	50.1	+1.7	−3.9
d(gcgttztttgct) (**ON4**)	48.8	+2.6	47.8	−0.6	+1.0

[a]UV melting profiles were measured in 10 mM sodium cacodylate buffer (pH 7.4) containing 100 mM NaCl at a scan rate of 0.5 °C/min at 260 nm. The concentration of the oligonucleotide was 1.5 μM for each strand (see also the Supporting Information). The T_m values are the average of at least three measurements. The sequences of ssDNA and ssRNA are 5′-d(agcaaaaaacgc)-3′ and 5′-r(AGCAAAAAACGC)-3′, respectively. **x** = LNA/BNA-T. **y** = 2′-deoxy-4′-thioT. **z** = 4′-thioLNA/BNA-T. ΔT_m, the change in T_m value compared to the unmodified standard strand (**ON1**).

for duplex formation (**ON3**/ssRNA: ΔT_m = −0.2 °C; **ON3**/ssDNA: ΔT_m = +1.7 °C). The results for **ON4** were different from those for **ON2** and **ON3**.

Thus, **ON4** increases the T_m value of +2.6 °C with ssRNA, while it decreases the T_m value of −0.6 °C with ssDNA; these results indicated that the 4′-thioLNA/BNA-modified ON has promising RNA selectivity for duplex formation. The RNA selectivity of the 4′-thioLNA/BNA-modified ON (**ON4**) for duplex formation (T_m(**ON4**/ssRNA) − T_m(**ON4**/ssDNA) = +1.0 °C) was superior to that of the LNA/BNA-modified ON (**ON2**) (T_m(**ON2**/ssRNA) − T_m(**ON2**/ssDNA) = −0.2 °C), although the ΔT_m value of **ON4** against ssRNA was smaller than that of **ON2**. This type of RNA selectivity is a typical and advantageous property of 2′-modified 4′-thioRNAs:[6] 2′-OMe-4′-thioRNA, 2′-F-4′-thioRNA, and 4′-thioLNA/BNA.

Next, we investigated the resistance against enzymatic digestion of each ON. The polythymidine ONs with the 3′-terminal residues modified with either LNA/BNA, 2′-deoxy-4′-thionucleoside or 4′-thioLNA/BNA (each 9-mer) were synthesized and incubated with 3′-exonuclease (Crotalus adamanteus venom phosphodiesterase, CAVP). The percentage of the remaining intact ONs was monitored over time (Figure 2). The natural polythymidine sequence (**ON5**) was completely degreased within 10 min, whereas the LNA/BNA-modified and 2′-deoxy-4′-thiomodified congeners (**ON6** and **ON7**) were hydrolyzed in 20 min. In contrast, modification with 4′-thioLNA/BNA enhanced the resistance against 3′-exonuclease-mediated digestion, with over 50% of the 4′-thioLNA/BNA-modified ON (**ON8**) remaining intact after 20 min.

In conclusion, we synthesized 4′-thioLNA/BNA monomers by the tandem ring-contraction-aldol reaction and the Pummerer-type thioglycosylation as key reactions. We also found a simple and unique reaction that could convert 4′-hydroxymethyl-4′-thionucleoside to the corresponding 4′-thioLNA/BNA monomer. The ON containing the 4′-thioLNA/BNA monomer showed high and selective hybridization ability with RNA. In addition, this ON is resistant against exonuclease digestion rather than LNA/BNA and 4′-thioDNA. Thus, 4′-thioLNA/BNA would be a new candidate for ON drug development.

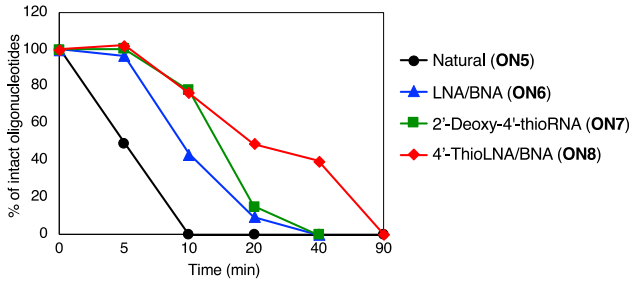

Figure 2. Stability of ONs against 3′-exonuclease-mediated digestion. Hydrolysis of oligonucleotides (1 nmol) assessed at 37 °C in buffer (150 μL) containing 50 mM Tris−HCl (pH 8.0), 10 mM $MgCl_2$, and CAVP (5.0 μg/mL). A portion of each reaction mixture was removed at timed intervals and heated to 90 °C for 5 min to deactivate the enzyme. The sequences of the ONs used were 5′-d(TTTTTTTTT)-3′. T = natural T (black circle, **ON5**), T = LNA/BNA-T (blue triangle, **ON6**), T = 2′-deoxy-4′-thioT (green square, **ON7**), and T = 4′-thioLNA/BNA-T (red diamond, **ON8**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01306.

Experimental information, detailed experimental procedures, additional schemes and figures, and copies of the spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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